Clinical Policy Bulletin: Tumor Scintigraphy

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Policy

ProstaScint

Aetna considers ProstaScint scans medically necessary for either of the following indications:

1. Pre-operative staging of newly diagnosed persons with biopsy-proven prostate cancer that is thought to be clinically localized after standard diagnostic evaluation, but who have a moderate to high probability of occult extra-prostatic metastasis; or

2. Staging of post-prostatectomy persons or persons treated with radiation therapy in whom there is a high suspicion of undetected residual prostate cancer or cancer recurrence.

Aetna considers ProstaScint scans experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

Oncoscint

Aetna considers monoclonal antibody (MAb) imaging (also known as radioimmunoscinctigraphy and Oncoscint immunoscintigraphy) using satumomab pendetide medically necessary for any of the following indications:

1. As an alternative to second-look laparotomy to detect occult colorectal carcinoma in persons with suspected recurrence suggested by an elevated carcino-embryonic antigen (CEA) level, but who have no evidence of disease on conventional imaging modalities (including CT scan); or

2. Detection of occult colorectal carcinoma in persons about to undergo a potentially curative resection of an apparently isolated recurrence located at a single site (e.g., lung or liver) which has been identified on conventional imaging modalities (including CT scan) and for whom the detection of occult lesions elsewhere would alter the surgical management; or
3. Detection of occult recurrent ovarian cancer in persons with suspected recurrence suggested by rising tumor markers, when no other imaging or physical examination technique can locate the suspected disease.

Aetna considers Oncoscnt immunoscintigraphy experimental and investigational for all other indications such as any of the following because it has not been established to have a clearly defined role in the management of individuals with these indications:

1. As a screening tool for cancers; or
2. Detection of occult disease in persons who have melanoma, breast cancer, thrombosis, inflammatory disease, lymphoma, or prostate cancer because there are insufficient scientific data to document the clinical utility of Oncoscnt immunoscintigraphy in the management of persons with these conditions; or
3. In other colorectal cancer persons not meeting criteria #1 or #2 above (for instance, post-operative colorectal cancer persons with rising serum CEA levels and negative standard imaging and other studies.

CEA-Scan

Aetna considers CEA-Scan® using Tc-99m-arcitumomab, a radiodiagnostic agent produced by Immunomedics, for use in conjunction with computerized tomography (CT) scans medically necessary for detection of recurrent or metastatic colorectal cancer in the liver and extra-hepatic abdomen and pelvis. Aetna considers the CEA-scan experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

Technetium-99m-Sestamibi Scintigraphy

Aetna considers technetium-99m-sestamibi (Tc-MIBI) scintigraphy medically necessary for any of the following indications:

1. For assessment malignant bone and soft tissue tumor response to therapy; or
2. For evaluation of metastatic thyroid cancer; or
3. For evaluation of parathyroid adenoma. (Note: Technetium tc-99m pertechnetate (thallium) subtraction scan with technetium tc-99m sestamibi scan for parathyroid adenoma is considered medically necessary)

Aetna considers technetium-99m-sestamibi scintigraphy experimental and investigational for all other indications such as the following because its role for these indications has not been established:

1. For detection of malignant axillary adenopathy secondary to breast cancer; or
2. For evaluation of central nervous system (CNS) neoplasms; or
3. For imaging of breast cancer (known as Miraluma scan).

Octreoscan

Aetna considers an Octreoscan, using octreotide (Sandostatin) tagged with radiolabeled $^{111}$Indium-pentetreotide, medically necessary for the diagnosis and staging of persons with primary and metastatic neuroendocrine tumors bearing somatostatin receptors. Such tumors include any of the following:

Carcinoid tumors/carcinoid syndrome
Gastrinomas
Glucagonomas
Insulinomas
Islet cell tumors of the pancreas
Medullary thyroid carcinoma (MTC)
Neuroendocrine carcinoma of the rectum
Paragangliomas
Pheochromocytomas
Pituitary adenomas
Tumor-induced osteomalacia (oncogenic osteomalacia) (for diagnosis only)
VIPoma (vasoactive intestinal peptide) -- persons present with Verner-Morrison syndrome: watery diarrhea, hypokalemia and achlorhydria

Aetna considers $^{111}$In-pentetreotide (OctreScan) experimental and investigational for all other indications such as any of the following because the sensitivity and specificity of this test for the following indications has been demonstrated to be inadequate:

Astrocytomias
Chemodectomas
Hodgkin lymphoma
Meningiomas
Neuroblastoma (olfactory, mediastinal)
Merkel cell tumors
Non-Hodgkin’s lymphoma
Ocular melanoma
Sarcoidosis
Small-cell lung cancer, primary or metastatic
Thymoma

Radiolabeled Octreotide for Therapeutic Use

Aetna considers radiolabeled octreotide medically necessary for the treatment of gastroenteropancreatic neuroendocrine tumors. The gamma emitting imaging radionuclide ($^{111}$In-octreotate) is replaced by a beta imaging therapy radionuclide (90Y-octreotide). Guidelines from the UKNETwork for Neuroendocrine Tumours (Ramage et al, 2005) state that targeted radionuclide therapy, including 90Y-octreotide (also known as 90Y-DOTATOC), is a useful palliative option for symptomatic individuals with inoperable or metastatic gastroenteropancreatic neuroendocrine tumors where there is corresponding abnormally increased uptake of the corresponding radionuclide imaging agent.

Aetna considers radiolabeled octreotide experimental and investigational for the treatment of incompletely resected meningioma because its effectiveness for this indication has not been established.

Lymphoscintigraphy and Sentinel Lymph Node Biopsy

Aetna considers lymphoscintigraphy and sentinel lymph node biopsy (SLNB) medically necessary for persons with malignant melanoma. In addition, Aetna considers radioactive
colloid and/or blue dye identification of the sentinel node in the axilla followed by SLNB medically necessary for persons with breast cancer. Lymphoscintigraphy and SLNB is considered experimental and investigational for all other indications (e.g., as a screening test in persons with a BRCA mutation, with or without prophylactic mastectomy) because its effectiveness for indications other than the ones listed above has not been established.

**Meta-Iodobenzylguanidine (MIBG) Imaging**

Aetna considers I-131 labeled meta-iodobenzylguanidine (MIBG, also known as iobenguane I-131) imaging medically necessary for localizing or confirming any of the following conditions:

- Adrenal medulla hyperplasia
- Carcinoid tumors
- Neuroblastoma
- Paraganglioma
- Pheochromocytoma
- Thyroid carcinoma.

Aetna considers I-123 labeled MIBG imaging experimental and investigational in the management of all conditions, such as any of the following, because its value for these indications has not been established:

- Arrhythmia
  - Arrhythmogenic right ventricular cardiomyopathy
  - Cardiomyopathy
  - Congestive heart failure (CHF)
  - Diabetes mellitus
  - Differentiating Parkinson's disease from multiple system atrophy or progressive supranuclear palsy
  - Drug-induced cardiotoxicity
  - Heart transplantation
  - Hypertension
  - Idiopathic ventricular fibrillation
  - Ischemic heart disease
  - Tracking response to medications for members with CHF

Aetna considers I-131 labeled MIBG radiotherapy experimental and investigational as a treatment for neuroblastoma, pheochromocytoma and all other indications because its effectiveness for these indications has not been established.

**AndreView**

Aetna considers iobenguane I-123 injection (AndreView, GE Healthcare) medically necessary for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests. Aetna considers iobenguane I-123 injection experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

**Scintimammography and Breast Specific Gamma Imaging (BSGI)**

Aetna considers scintimammography, including breast-specific gamma imaging (BSGI; also known as molecular breast imaging), experimental and investigational as an adjunct
to mammography for imaging of breast tissue, for the detection of axillary metastases, staging the axillary lymph nodes in members with breast cancer, and to assess response to adjuvant chemotherapy in members with breast cancer, and for all other indications because its effectiveness has not been established.

Technetium-Tc 99m Tilmanocept (Lymphoseek)

Aetna considers technetium Tc 99m tilmanocept (Lymphoseek) injection medically necessary for location of lymph nodes in persons with breast cancer or melanoma who are undergoing surgery to remove tumor-draining lymph nodes.

Aetna considers technetium Tc 99m tilmanocept injection experimental and investigational for all other indications (e.g., oral cavity squamous cell carcinoma)

**Background**

Nuclear imaging is assuming an increasing role in the management of patients with cancer. Tumor scintigraphy involves the intravenous administration of a radiopharmaceutical, defined as an isotope attached to a carrier molecule, which localizes in certain tumor tissues and the subsequent imaging and computer acquisition of data. The goal of tumor scintigraphy is to enable the interpreting physician to detect and evaluate primary, metastatic, or recurrent tumor tissue by producing images of diagnostic quality. In general, tumor scintigraphy may be used for, but is not limited to, detection of certain primary, metastatic, and recurrent tumors, evaluation of abnormal imaging and non-imaging findings in patients with a history of certain tumors, and reassessment of patients for residual tumor burden after therapy. Specific clinical applications differ depending upon the specific radiopharmaceutical that is used.

Traditional imaging modalities (CT, MRI) for prostate cancer perform very poorly and bone scanning, although having a high positive predictive value, is insensitive for metastasis and is used only in those patients with a reasonable probability of metastatic disease (e.g., prostate-specific antigen [PSA] greater than 10). The ProstaScint scan uses a monoclonal antibody-based imaging agent (In111-Capromab Pendetide) and was approved by the U.S. Food and Drug Administration (FDA) for use in patients with biopsy proven prostate cancer in whom there is a high clinical suspicion of occult metastatic disease and who have had a negative or equivocal standard staging evaluation.

Patients with primary colorectal carcinoma undergo an extensive pre-operative staging work-up. Unfortunately, the accuracy of non-surgical staging techniques (CT or MRI) has been shown to be poor. Recurrent disease is seen in up to 40% of patients with Dukes stage B or C colorectal carcinoma, generally within the first 18 months post-operatively. Carcinoembryonic antigen (CEA) levels are used to monitor patients for recurrent disease; however, almost 1/3 of patients with recurrence do not have elevated CEA levels. Both CT and MRI have been shown to be inadequate in the detection of local or lymph node recurrence. In regards to ovarian cancer, serum CA-125 levels have been shown to be useful in predicting the presence of ovarian cancer, but negative titers do not preclude malignancy. In clinical trials, OncoScint has a sensitivity of 70% versus 44% for CT, and a specificity of 55% (79% for CT) in patients with ovarian cancer. Carcinomatosis was detectable by antibody imaging in 71% of patients, but in only 45% by CT.
Oncoscint is an IgG murine monoclonal antibody that specifically targets the cell surface mucin-like glycoprotein antigen TAG-72, which is commonly found on colorectal and ovarian carcinomas. It is reported to be reactive with 83 % of colorectal carcinomas and 97 % of ovarian carcinomas. According to the available literature, a major advantage of Oncoscint is that it allows one to survey the entire body, thus permitting the detection of occult metastases that can have a major impact on tumor staging. Clinical studies have documented only minimal cross reactivity with other tumors or normal tissues (i.e., the false-positive rate is very low). Additionally, the results of the Oncoscint exam have been reported to result in a change in patient management in 25 % of cases, and the examination also detected sites of occult disease in 10 % of patients. Oncoscint can also be used to confirm the absence of other sites of disease prior to surgery. This is important for the patient about to undergo a potentially curative resection of an isolated recurrence of colorectal carcinoma located in a single site, i.e., lung or liver.

CEA-Scan is a nuclear imaging test which uses a monoclonal antibody fragment (arcitumomab) labeled with technetium 99 that reacts with CEA, a tumor marker for cancer of the colon and rectum. CEA-Scan can be used to detect recurrent or metastatic colorectal carcinoma in conjunction with standard imaging modalities. The agent is not indicated as a screening tool for colorectal cancer. The sensitivity of CEA-Scan has been shown to be superior to conventional imaging modalities in evaluation of the extra-hepatic abdomen (55 % versus 32 %) and pelvis (69 % versus 48 %). The scan findings are not superior to conventional exams in evaluation of the liver (63 % versus 64 %); however, the findings are often complementary. Lesion detection is in part related to lesion size, with a sensitivity of 80 % for lesions over 2 cm. Detection of lesions smaller than 1 cm is 60 %. CEA-Scan has been shown to have potential clinical benefit in 1/3 of colorectal cancer patients.

Since its introduction, technetium-99m-sestamibi (also known as technetium-99m-MIBI) has been shown to be of value in assessing malignant bone and soft tissue tumor response to therapy. Technetium-99m-sestamibi (Miraluma) has also been proposed as the radio-pharmaceutical agent for use during scintimammography in the evaluation of women with dense breast tissue and possibly for women who have had partial mastectomy, previous biopsies, radiation therapy or silicone implants. Although Miraluma may be more sensitive than thallium in the evaluation of breast lesions greater than 1.5 cm in size and was approved in May, 1997 by the FDA for use as a nuclear medicine test to be used in breast imaging, the reported sensitivities and specificities of Miraluma imaging vary based on size and the palpable nature of the finding. There is a lack of evidence in the medical literature demonstrating an acceptable level of sensitivity and specificity in detecting small, non-palpable breast lesions less than 1.2 cm, with or without microcalcification. Overall, Miraluma has a sensitivity of 83 to 96 % (average 85 %) and a specificity of 72 to 100 % (average 81 %) for malignancy. The negative predictive value has been reported to be between 88 to 97 %. False-positive examinations have been described with fibroadenomas, papillomas, epithelial hyperplasia, and fibrocystic breast disease. Patients with fibrocystic disease are more likely to have false-positive examinations even though the Miraluma exam has been reported to be unaffected by the density of the breast. Most false-negative examinations occur with lesions smaller than 1 cm in size or in lesions not palpable. Studies now indicate that the examinations sensitivity drops to 51 % to 72 % for non-palpable lesions. And lastly, the available literature shows that Miraluma is not competitive with mammography on either a cost-effective or sensitivity basis in the screening of patients for breast cancer.
All articles regarding Tc-MBI in the evaluation of breast masses suffer from 2 major drawbacks: (i) the reported results for these studies focuses on a pre-selected patient population resulting in a very high incidence of cancer in the patients sent for the examination. This suggests a selection bias and sensitivity of the examination is likely over-estimated; and (ii) the mean lesion size is generally over 1.0 to 1.5 cm where mammographic findings can aid in differentiating a benign from a malignant lesion. Other drawbacks include the lack of an adequately high negative predictive value, which means malignant lesions may be missed, and false positive exams occur in benign lesions such as fibroadenomas. Since the implications of a missed diagnosis of breast cancer can be disastrous to patient outcome, the available literature states that Miraluma has no role in breast cancer screening to confirm the presence or absence of malignancy (particularly clinically occult abnormalities), and it is not an alternative to biopsy. Stereotactic and ultrasound guided biopsies of breast lesions are minimally invasive and can provide a definitive diagnosis. Despite optimism in the nuclear medicine literature, the literature on balance states that this examination probably has no role in the evaluation of patients with suspected breast malignancy. Determining a subset of women that would benefit from this procedure will be difficult until larger prospective studies have been performed. Mammography remains the generally accepted standard for screening. Continued evaluation with diagnostic mammography, ultrasound and surgical biopsy remains the diagnostic work-up that is most frequently recommended. The Institute of Medicine of the National Academy of Science recently concluded that “scintimammography has shown diagnostic potential as an adjunct to mammography, but the technical limitations such as resolution have precluded it from becoming more widely used. Although it has FDA approval, the current data do not justify its implementation on a standard basis. Technological improvements and novel radioactive compounds could potentially improve its utility, but at the moment its future is uncertain. The method also has potential for use in functional imaging applications, but further study and development are needed.”

An assessment prepared for the Agency for Healthcare Research and Quality (Bruening et al, 2006) concluded that scintimammography is not sufficiently accurate to rule out breast cancer in women with abnormal mammograms or physical findings suggestive of breast cancer. The report found that, for every 1,000 women with negative scintimammogram results, about 907 women would avoid an unnecessary biopsy but 93 women would have missed cancers.

Scintimammography utilizing high-resolution gamma cameras (e.g., Dilon Scan/Dilon 6800 camera, Dilon Technologies, LLC, Newport News, VA), also known as breast-specific gamma imaging (BSGI), has a spatial resolution of less than 4 mm and is being marketed to help identify cancerous breast tissue that is undetected by mammography. Proponents believe this technology is useful as a complementary tool in the detection of breast cancer in women with difficult to read mammograms, such as those with dense breast tissue, breast implants or scar tissue from previous breast surgery. According to the advocates of this technology, by operating on a cellular or molecular level, BSGI is not affected by tissue density and can help detect cancers at very early stages and allow for optimal intervention and treatment. Its ability to accurately detect breast cancer has the potential to significantly reduce the number of unnecessary, invasive biopsies.

Brem and colleagues have published several comparative studies on the use of BSGI for the diagnosis of breast cancer. In one comparative study, Brem et al (2007) compared the sensitivity of BSGI for the detection of ductal carcinoma in situ (DCIS) with the results
obtained with mammography and magnetic resonance imaging (MRI) based on the histopathology of biopsy-proven DCIS. After injection of technetium 99m-sestamibi, patients had BSIGI in craniocaudal and mediolateral oblique projections. Imaging findings were compared to findings at biopsy or surgical excision. Breast MRI was performed on 7 patients with 8 biopsy-proven foci. Pathologic tumor size of the DCIS ranged from 2 to 21 mm (mean of 9.9 mm). Of 22 cases of biopsy-proven DCIS in 20 women, 91% were detected with BSIGI, 82% were detected with mammography, and 88% were detected with MRI. The authors reported that BSIGI had the highest sensitivity for the detection of DCIS, although the small sample size did not demonstrate a statistically significant difference. Two cases of DCIS (9%) were diagnosed only after BSIGI demonstrated an occult focus of radiotracer uptake in the contralateral breast, previously undetected by mammography and there were 2 false-negative BSIGI studies. In another study, Brem and colleagues (2008) reported the sensitivity and specificity of BSIGI for the detection of breast cancer using pathologic results as a reference standard as 96.4% and 59.5%, respectively, a positive predictive value of 68%, and a negative predictive value of 94% for non-malignant lesions. The smallest invasive cancer and DCIS detected by BSIGI was reported to be 1 mm.

In a retrospective review, Zhou et al (2008) reported the results of BSIGI on 176 patients who underwent BSIGI evaluation. A total of 128 patients underwent BSIGI because of suspicious imaging, abnormal physical examination, or were considered high risk for breast cancer with dense breasts. BSIGI was positive in 12 of 107 patients with breast imaging reporting and data system (BI-RADS) 1, 2, or 3. Two of these were cancer. Of the 21 patients with BI-RADS 4, 18 were BSIGI-negative (11 with benign biopsy, 7 observed), and 3 were BSIGI-positive with 2 being cancerous. Forty-eight patients with a new diagnosis of cancer obtained BSIGI for further work-up. It was positive at a new location in 6 cases: 2 cases were new cancers in the contralateral breast, 1 was in the ipsilateral breast, and the remaining 3 had benign pathology. The authors reported that clinical management was changed significantly in 14.2% of the 176 patients, with another 6.3% in whom a negative BSIGI could have prevented a biopsy. The authors concluded, "Potential roles for BSIGI in the current paradigm of breast imaging include screening and diagnosis. BSIGI has the ability to pick up mammography occult breast cancers and can be especially useful in high-risk patients with dense breasts in whom the sensitivity and specificity of mammography suffers significantly. Another promising use of BSIGI could be further evaluation of BI-RADS 4 patients to see if invasive biopsy can be avoided. A larger series of patients is needed to confirm this hypothesis."

Recent studies of scintimammography utilizing BSIG are promising; however, patient populations were small and focused on a pre-selected patient population resulting in a very high incidence of cancer in the patients sent for examination. This suggests a selection bias and sensitivity of the examination is likely over-estimated. In addition, there are no studies that evaluate change in clinical practice if the breast-specific gamma camera was used in stead of, or in addition to, MRI or ultrasound, and its impact on clinical outcomes. The effectiveness of scintimammography in screening or diagnostic strategies needs to be evaluated in large-scale clinical trials.

The American College of Radiology (ACR) and Society for Pediatric Radiology (SPR)'s practice guideline for the performance of tumor scintigraphy (with gamma cameras) (2010) stated that "more recently, breast-specific gamma imaging (BSIGI) which uses a high-resolution, small-field-of-view gamma camera optimized to image breast tumors has been developed. Areas of active investigation concerning potential indications include
determination of extent of disease in women with newly diagnosed breast cancer, and evaluation of patients with dense breasts. Additional clinical evidence is needed to assess where BSGI will fit in the imaging algorithm of breast cancer. When BSGI is performed, the ability to correlate BSGI findings with other breast imaging techniques and a defined protocol for evaluation of abnormalities seen only on BSGI should be in place.

O'Connor and associates (2010) noted that recent studies have raised concerns about exposure to low-dose ionizing radiation from medical imaging procedures. Little has been published regarding the relative exposure and risks associated with breast imaging techniques such as BSGI, molecular breast imaging (MBI), or positron emission mammography (PEM). The purpose of this article was to estimate and compare the risks of radiation-induced cancer from mammography and techniques such as PEM, BSGI, and MBI in a screening environment. The authors used a common scheme for all estimates of cancer incidence and mortality based on the excess absolute risk model from the BEIR VII report. The lifetime attributable risk model was used to estimate the lifetime risk of radiation-induced breast cancer incidence and mortality. All estimates of cancer incidence and mortality were based on a population of 100,000 females followed from birth to age 80 and adjusted for the fraction that survives to various ages between 0 and 80. Assuming annual screening from ages 40 to 80 and from ages 50 to 80, the cumulative cancer incidence and mortality attributed to digital mammography, screen-film mammography, MBI, BSGI, and PEM was calculated. The corresponding cancer incidence and mortality from natural background radiation was calculated as a useful reference. Assuming a 15 % to 32 % reduction in mortality from screening, the benefit/risk ratio for the different imaging modalities was evaluated. Using conventional doses of 925 MBq Tc-99m sestamibi for MBI and BSGI and 370 MBq F-18 FDG for PEM, the cumulative cancer incidence and mortality were found to be 15 to 30 times higher than digital mammography. The benefit/risk ratio for annual digital mammography was greater than 50:1 for both the 40 to 80 and 50 to 80 screening groups, but dropped to 3:1 for the 40 to 49 age group. If the primary use of MBI, BSGI, and PEM is in women with dense breast tissue, then the administered doses need to be in the range 75 to 150 MBq for Tc-99m sestamibi and 35 MBq to 70 MBq for F-18 FDG in order to obtain benefit/risk ratios comparable to those of mammography in these age groups. These dose ranges should be achievable with enhancements to current technology while maintaining a reasonable examination time. The authors concluded that the results of the dose estimates in this study clearly indicate that if molecular imaging techniques are to be of value in screening for breast cancer, then the administered doses need to be substantially reduced to better match the effective doses of mammography.

Kim (2012) evaluated the adjunctive benefits of BSGI versus MRI in breast cancer patients with dense breasts. This study included a total of 66 patients (44.1 +/- 8.2 years) with dense breasts (breast density greater than 50 %) and already biopsy-confirmed breast cancer. All of the patients underwent BSGI and MRI as part of an adjunct modality before the initial therapy. Of 66 patients, the 97 undetermined breast lesions were newly detected and correlated with the biopsy results. Twenty-six of the 97 breast lesions proved to be malignant tumors (invasive ductal cancer, n = 16; DCIS, n = 6; mixed or other malignancies, n = 4); the remaining 71 lesions were diagnosed as benign tumors. The sensitivity and specificity of BSGI were 88.8 % (confidence interval (CI): 69.8 to 97.6 %) and 90.1 % (CI: 80.7 to 95.9 %), respectively, while the sensitivity and specificity of MRI were 92.3 % (CI: 74.9 to 99.1 %) and 39.4 % (CI: 28.0 to 51.7 %), respectively (p < 0.0001). MRI detected 43 false-positive breast lesions, 37 (86.0 %) of which were correctly diagnosed as benign lesions using BSGI. In 12 malignant lesions less than 1
cm, the sensitivities of BSGI and MR imaging were 83.3 % (CI: 51.6 to 97.9 %) and 91.7 % (CI: 61.5 to 99.8 %), respectively. The author concluded that BSGI showed an equivocal sensitivity and a high specificity compared to MRI in the diagnosis of breast lesions. In addition, BSGI had a good sensitivity in discriminating breast cancers less than or equal to 1 cm. The results of this study suggested that BSGI could play a crucial role as an adjunctive imaging modality which can be used to evaluate breast cancer patients with dense breasts.

Keto et al (2012) prospectively compared the sensitivity of BSGI to MRI in newly diagnosed ductal carcinoma-in-situ (DCIS) patients. Patients with newly diagnosed DCIS from June 1, 2009, through May 31, 2010, underwent a protocol with both breast MRI and BSGI. Each imaging study was read by a separate dedicated breast radiologist. Patients were excluded if excisional biopsy was performed for diagnosis, if their MRI was performed at an outside facility, or if final pathology revealed invasive carcinoma. There were 18 patients enrolled onto the study that had both MRI and BSGI for newly diagnosed DCIS. The sensitivity for MRI was 94 % and for BSGI was 89 % (p > 0.5, NS). There was 1 index tumor not seen on either MRI or BSGI, and 1 index tumor seen on MRI but not visualized on BSGI. The authors concluded that although BSGI has previously been shown to be as sensitive as MRI for detecting known invasive breast carcinoma, this study shows that BSGI is equally as sensitive as MRI at detecting newly diagnosed DCIS. They stated that as a result of the limited number of patients enrolled onto the study, larger prospective studies are needed to determine the true sensitivity and specificity of BSGI.

Spanu et al (2012) investigated the clinical impact of breast scintigraphy acquired with a breast specific γ-camera (BSGC) in the diagnosis of breast cancer (BC) and assessed its incremental value over mammography (Mx). A consecutive series of 467 patients underwent BSGC scintigraphy for different indications: suspicious lesions on physical examination and/or on US/MRI negative at Mx (BI-RADS 1 or 3), characterization of lesions suspicious at Mx (BI-RADS 4), pre-operative staging in lesions highly suggestive of malignancy at Mx (BI-RADS 5). Definitive histopathological findings were obtained in all cases after scintigraphy: 420/467 patients had BC, while 47/467 patients had benign lesions. The scintigraphic data were correlated to Mx BI-RADS category findings and to histology. The incremental value of scintigraphy over Mx was calculated. Scintigraphy was true-positive in 97.1 % BC patients, detecting 96.2 % of overall tumor foci, including 91.5 % of carcinomas less than or equal to 10 mm, and it was true-negative in 85.1 % of patients with benign lesions. Scintigraphy gave an additional value over Mx in 141/467 cases (30.2 %). In particular, scintigraphy ascertained BC missed at Mx in 31 patients with BI-RADS 1 or 3, including 26 patients with heterogeneously/high dense breast (19/26 with tumors less than or equal to 10 mm) and detected additional clinically occult ipsilateral or contralateral tumor foci (all less than 10 mm) or the in-situ component sited around invasive tumors in 77 BC patients with BI-RADS 4 or 5, changing surgical management in 18.2 % of these cases; moreover, scintigraphy ruled out malignancy in 33 patients with BI-RADS 4. BSGC scintigraphy proved a highly sensitive diagnostic tool, even in small size carcinoma detection, while maintaining a high specificity. The procedure increased the sensitivity of Mx, especially in dense breast and in multi-focal/multi-centric disease, as well as the specificity. It better defined local tumor extension, thus guiding the surgeon to a more appropriate surgical treatment. Moreover, these researchers stated that "However, also this scintigraphic procedure presents some limitations, such as radiation exposure that could limit its routine use, especially in screening programs. Tumor size seemed to represent the most important factor affecting the performance of scintigraphy, since the majority of false-negative findings were related
to sub-centimetric carcinomas. Moreover, lesion site may also affect sensitivity, since a high percentage of small tumors negative at breast scintigraphy in our series were located in internal quadrants or were excluded from the field of view of the device as happened in two cases .... A larger clinical application of BSGC scintigraphy is thus suggested although many prospective trials are needed, particularly with the aim of identifying those subgroups of patients who would more benefit from scintigraphy employment .... However, cost-benefit analysis is needed to justify the use of BSGC scintigraphy in combination with conventional diagnostic imaging methods as an adjunctive tool".

Mitchell et al (2013) determined the ability of breast imaging with 99mTc-sestamibi and a direct conversion- MBI system to predict early response to neoadjuvant chemotherapy (NAC). Patients undergoing NAC for breast cancer were imaged with a direct conversion-MBI system before (baseline), at 3 to 5 weeks after onset, and after completion of NAC. Tumor size and tumor-to-background (T/B) uptake ratio measured from MBI images were compared with extent of residual disease at surgery using the residual cancer burden. A total of 19 patients completed imaging and proceeded to surgical resection after NAC. Mean reduction in T/B ratio from baseline to 3 to 5 weeks for patients classified as RCB-0 (no residual disease), RCB-1 and RCB-2 combined, and RCB-3 (extensive residual disease) was 56 % (SD, 0.20), 28 % (SD, 0.20), and 4 % (SD, 0.15), respectively. The reduction in the RCB-0 group was significantly greater than in RCB-1/2 (p = 0.036) and RCB-3 (p = 0.001) groups. The area under the receiver operator characteristic curve for determining the presence or absence of residual disease was 0.88. Using a threshold of 50 % reduction in T/B ratio at 3 to 5 weeks, MBI predicted presence of residual disease at surgery with a diagnostic accuracy of 89.5 % (95 % confidence interval [CI]: 0.64 % to 0.99 %), sensitivity of 92.3 % (95 % CI: 0.74 % to 0.99 %), and specificity of 83.3 % (95 % CI: 0.44 % to 0.99 %). The reduction in tumor size at 3 to 5 weeks was not statistically different between RCB groups. The authors concluded that changes in T/B ratio on MBI images performed at 3 to 5 weeks following initiation of NAC were accurate at predicting the presence or absence of residual disease at NAC completion. They stated that "A limitation of MBI is its inability to depict axillary node involvement and potentially to visualize tumors close to the chest wall .... Our results are promising, but larger studies evaluating the use of 99mTc-sestamibi and dedicated gamma cameras are needed to support these findings".

Hruska and colleagues (2014) compared diagnostic performance of MBI performed with standard 10-min-per-view acquisitions and half-time 5-min-per-view acquisitions, with and without wide beam reconstruction (WBR) processing. A total of 82 bilateral, 2-view MBI studies were reviewed. Studies were performed with 300 MBq Tc-99 m sestamibi and a direct conversion MBI (DC-MBI) system. Acquisitions were 10 min-per-view; the first half of each was extracted to create 5-min-per-view datasets, and WBR processing was applied. The 10-min-, 5-min-, and 5-min-per-view WBR studies were independently interpreted in a randomized, blinded fashion by 2 radiologists. Assessments of 1 to 5 were assigned; 4 and 5 were considered test positive. Background parenchymal uptake, lesion type, distribution of non-mass lesions, lesion intensity, and image quality were described. Considering detection of all malignant and benign lesions, 5 min-per-view MBI had lower sensitivity (mean of 70 % versus 85 % (p ≤ 0.04) for 2 readers) and lower area under curve (AUC) (mean of 92.7 versus 99.6, p ≤ 0.01) but had similar specificity (p = 1.0). WBR processing did not alter sensitivity, specificity, or AUC obtained at 5 min-per-view. Overall agreement in final assessment between 5-min-per-view and 10-min-per-view acquisition types was near perfect (κ = 0.82 to 0.89); however, fair-to-moderate agreement was observed for assessment category 3 (probably benign) (κ = 0.24 to 0.48).
Of 33 malignant lesions, 6 (18%) were changed from assessment of 4 or 5 with 10-min-per-view MBI to assessment of 3 with 5-min-per-view MBI. Image quality of 5-min-per-view studies was reduced compared to 10-min-per-view studies for both readers (3.24 versus 3.98, p < 0.0001 and 3.60 versus 3.91, p < 0.0001). WBR processing improved image quality for 1 reader (3.85 versus 3.24, p < 0.0001). The authors concluded that although similar radiologic interpretations were obtained with 10-min- and 5-min-per-view DC-MBI, resulting in substantial agreement in final assessment, notable exceptions were found: (i) perceived image quality at 5 min-per-view was lower than that for 10-min-per-view studies and (ii) in a number of cases, assessment was down-graded from a recommendation of biopsy to that of short interval follow-up. These investigators stated that “A limitation of this study was that most patients had either photopenic or mild background uptake; only 4 patients (8 breasts) were assigned moderate or marked background uptake. All lesions downgraded at 5 min-per-view were in patients with photopenic or mild background uptake. Hence, the effect of moderate or marked background parenchymal uptake on lesion detection at 5 min-view could not be assessed in this study. An additional limitation was that the detection task was a combined detection and characterization process. Lesions, when identified, were done so using the BI-RADSi-like assessment scale at the breast level. A subtlety of this analysis is that breasts characterized as 3 were treated as screen failures (MBI negative as a test result with a binary decision).”

Neuroendocrine tumors generally are small and slow-growing in nature, which makes them difficult to detect and localize using conventional imaging techniques such as CT and MRI. Octreotide (Octreotide In-111) is a synthetic octapeptide analog of somatostatin that binds to somatostatin receptors on cell surfaces throughout the body. The Octreoscan, which uses this radiopharmaceutical, can assist in staging the patient's disease more accurately by offering highly sensitive, whole-body detection and localization of primary and metastatic receptor-bearing neuroendocrine tumors, especially if they are small. Octreotide has been shown to have an overall sensitivity of about 96% in the detection of carcinoid tumors. The literature indicates that, before consideration of aggressive cytoreductive hepatic surgery, an Octreoscan can be used for ruling out extrahepatic metastases. As a consequence of the ability of Octreoscan to demonstrate somatostatin receptor-positive tumors, it can be used to select those patients who are likely to respond favorably to octreotide treatment. Finally, the literature states that a negative Octreoscan implies that the tumors are not expressing somatostatin receptors; this is often associated with a more anaplastic histology.

There is currently insufficient evidence to support the use of Octreoscan for patients with granulomatous diseases (e.g., sarcoidosis). In particular, guidelines from the Society for Nuclear Medicine (2004) stated that gallium scintigraphy is used to localize inflammation in sarcoidosis.

Carbone and colleagues (2003) examined Octreoscan scintigraphy as a tool for classifying and assessing disease activity in sarcoidosis and idiopathic interstitial pneumonia (IIP), in comparison of the radiological imaging and dyspnea symptom scores. A total of 33 patients of which 16 with sarcoidosis (mean age of 43.6 years, range of 30 to 58 years) and 17 with histologically diagnosed IIP (mean age of 62.2 years, range of 35 to 79 years) were enrolled in the study. Clinical history was taken as well as physical examination, chest X-ray, and pulmonary function tests were assessed. A high-resolution computed tomography scan (HRCT) was carried out in patients affected by sarcoidosis, who had a normal chest X-ray, and in IIP patients. Both groups were evaluated with the
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Octreoscan uptake index (UI; normal value: less than or equal to 10). In patients affected with sarcoidosis, the Octreoscan UI was significantly higher than in patients with IIP (16.35 +/- 3.1 and 10.06 +/- 0.8, respectively; p < 0.01) and was correlated with the radiographical staging (p < 0.01) and with the degree of dyspnea (p < 0.01). In patients with IIP, the Octreoscan UI was slightly above the normal limit (range of 10.3 to 11.7) in non-specific interstitial pneumonia (NSIP) and desquamative interstitial pneumonia (DIP), whereas in usual interstitial pneumonia (UIP) Octreoscan UI was always within normal limit (less than or equal to 10 UI). A negative correlation was observed with histological findings (p < 0.01) and with HRCT appearance (p < 0.01). The authors concluded that Octreoscan UI is correlated with the degree of dyspnea in patients affected by sarcoidosis and can quantify more accurately the degree of pulmonary involvement, as compared to radiological assessment. Moreover, they stated that further studies are needed to evaluate Octreoscan as an early test for predicting disease progression.

Kroot et al (2006) reported on a case in which sarcoidosis in a clinically unaffected joint was demonstrated by somatostatin receptor scintigraphy. The patient presented with decreased hearing, secondary amenorrhea, vertigo, dry eyes, and progressive loss of vision. Because the differential diagnosis consisted of sarcoidosis and lymphoma, somatostatin receptor scintigraphy with indium-111-DTPA octreotide was performed. Increased uptake was observed in the parotid gland, bilateral orbits, nose, and the right knee. Remarkably, on clinical examination, no signs of arthritis of the right knee were observed. Additional tissue analysis of the right knee revealed the diagnosis of sarcoidosis leading to successful treatment with prednisolone, anti-malarials, and azathioprine. This case underlines the diagnostic potential of somatostatin receptor scintigraphy in patients with sarcoidosis, even in clinically unaffected tissue.

Radiolabeled octreotide is also being studied for the treatment of radio-resistant solid tumors especially small tumors (a few millimeters in diameter) whose uptake is maximal, allowing more homogeneous distribution than that achieved with large tumors. The gamma emitting imaging radionuclide (111In-octreotate) is replaced by a beta emitting therapeutic radionuclide (90Y-octreotide) (OctreoTher). Guidelines from the UKNETwork for Neuroendocrine Tumours (Ramage et al, 2005) state that targeted radionuclide therapy is a useful palliative option for symptomatic patients with inoperable or metastatic neuroendocrine tumors where there is corresponding abnormally increased uptake of the corresponding radionuclide imaging agent.

There are no randomized controlled clinical trials of targeted radionuclide therapy of neuroendocrine tumors. In a retrospective study (n = 21), Bodei and colleagues (2004) assessed the effectiveness of Yttrium-90 [90Y]-DOTA-Phe1-Tyr3-octreotide (90Y-DOTATOC) therapy in metastatic medullary thyroid cancer (MTC) patients with positive OctreoScan, progressing after conventional treatments. Two patients (10 %) obtained a complete response (CR), as evaluated by CT, MRI and/or ultrasound, while a stabilization of disease (SD) was observed in 12 patients (57 %); 7 patients (33 %) did not respond to therapy. The duration of the response ranged between 3 to 40 months. Using biochemical parameters (calcitonin and CEA), CR was observed in 1 patient (5 %), while partial response was observed in 5 patients (24 %) and stabilization in 3 patients (14 %). Twelve patients had progression (57 %); and CR was observed in patients with lower tumor burden and calcitonin values at the time of the enrollment. These investigators concluded that this retrospective analysis is consistent with the literature, regarding a low response rate in MTC treated with 90Y-DOTATOC. Patients with smaller tumors and higher uptake of the radiopeptide tended to respond better. Studies with 90Y-DOTATOC
administered in earlier phases of the disease will help to evaluate the ability of this
treatment to enhance survival.

Waldherr et al (2002) reported on a prospective phase II study to evaluate the tumor
response of neuroendocrine tumors to high-dose targeted irradiation with 90Y-
DOTATOC. A total of 39 patients with progressive neuroendocrine gastroentero-
pancreatic and bronchial tumors were treated with 4 intravenous injections of 90Y-
DOTATOC, administered at intervals of 6 weeks, and were followed for a median duration
of 6 months (range of 2 to 12 months). The investigators reported an objective response
rate of 23 %. For endocrine pancreatic tumors (13 patients), the objective response rate
was 38 %. Complete remissions were found in 5 % (2/39), partial remissions in 18 %
(7/39), stable disease in 69 % (27/39), and progressive disease in 8 % (3/39). The
investigators reported that a significant reduction of clinical symptoms could be found in
83 % of patients with diarrhea, in 46 % of patients with flushing, in 63 % of patients with
wheezing, and in 75 % of patients with pellagra. Side effects were grade 3 or 4
lymphocytopenia in 23 %, grade 3 anemia in 3 %, and grade 2 renal insufficiency in 3 %.

Paganelli et al (2002) reported on a study for 90Y-DOTATOC in 87 patients with
neuroendocrine tumors. The investigators stated that most patients responded with
stabilization of disease (48 %); however, objective responses were observed in 28 % of
patients, including 5 % of patients showing a complete response. The median duration
of response was 24 months. The investigators reported that gastrointestinal side effects
were mild and included nausea and vomiting, which occurred in approximately 50 % of
patients.

Weiner and Thakur (2005) noted that radiolabeled peptide therapy is usually indicated for
patients with widespread disease that is not amenable to focused radiation therapy or is
refractory to chemotherapy. Phase I and phase II studies using various radiolabeled
peptides (including (111)In-pentetreotide, 90Y-DOTATOC, 90Y-DOTA-lanreotide, and
Lutetium-177 [177Lu]-DOTA-octreotate) for the treatment of patients with neuroendocrine
malignancy are in progress. This is in agreement with the observations of Oberg and
Eriksson (2005) as well as Kwekkeboom and colleagues (2005). Oberg and Eriksson
stated that tumor-targeted treatment for malignant carcinoid tumor is still investigational,
but has become of significant interest with the use of radiolabeled somatostatin analogs.
(111)Indium-DTPA-octreotide has been used as the first tumor-targeted treatment, with
rather low response rates (in the order of 10 to 20 %) and no significant tumor shrinkage.
The second radioactive analog which has been applied in the clinic is 90Y-DOTATOC
(OctreoTher), which has given partial and complete remissions in 20 to 30 % of patients.
The most significant side effects have been kidney dysfunction, thrombocytopenia and
liver toxicity. Kwekkeboom et al noted that treatment with radiolabeled somatostatin
analogs is a promising new tool in the management of patients with inoperable or
metastasized neuroendocrine tumors. In a review of the literature on somatostatin
analogs in the treatment of gastroentero-pancreatic neuroendocrine tumors, Delaunoit
et al (2005) stated that overall, radiolabeled somatostatin analogues have shown some
activities in controlling tumor growth and clinical symptoms have been reduced
significantly. Toxic effects encountered have been manageable with adequate supportive
“constitute a promising alternative for treating patients with progressive and symptomatic
disease” and that “[t]he results of larger ongoing studies are eagerly awaited.”
In a phase II study, Johnson and colleagues (2011) evaluated the efficacy and safety of subcutaneous octreotide therapy for the treatment of recurrent meningioma and meningeal hemangiopericytoma. Octreotide is an agonist of somatostatin receptors, which are frequently expressed in meningioma, and reports have suggested that treatment with somatostatin agonists may lead to objective response in meningioma. Patients with recurrent/progressive meningioma or meningeal hemangiopericytoma were eligible for enrollment; those with atypical/anaplastic meningioma or hemangiopericytoma must have experienced disease progression despite radiotherapy or have had a contraindication to radiation. Patients received subcutaneous octreotide with a goal dose of 500 µg 3 times per day, as tolerated. Imaging was performed every 3 months during therapy. The primary outcome measure was radiographic response rate. Eleven patients with meningioma and 1 with meningeal hemangiopericytoma were enrolled during the period 1992 to 1998. Side effects included diarrhea (grade 1 in 4 patients and grade 2 in 2), nausea or anorexia (grade 1 in 4 patients), and transaminitis (grade 1 in 1 patient). One patient developed extra hepatic cholangiocarcinoma, which was likely unrelated to octreotide therapy. No radiographic responses were observed. Eleven of the 12 patients experienced progression, with a median time to progression of 17 weeks. Two patients experienced long progression-free intervals (30 months and greater than or equal to 18 years). Eleven patients have died. Median duration of survival was 2.7 years. Immunohistochemical staining of somatostatin receptor Sstr2a expression in a subset of patients did not reveal a correlation between level of expression and length of progression-free survival. Octreotide was well-tolerated but failed to produce objective tumor response, although 2 patients experienced prolonged stability of previously progressive tumors.

Schulz et al (2011) stated that the standard surgical treatment for meningiomas is total resection, but the complete removal of skull base meningiomas can be difficult for several reasons. Thus, the management of certain meningiomas of the skull base -- for example, those involving basal vessels and cranial nerves -- remains a challenge. In recent reports it has been suggested that somatostatin (SST) administration can cause growth inhibition of unresectable and recurrent meningiomas. The application of SST and its analogs is not routinely integrated into standard treatment strategies for meningiomas, and clinical studies proving growth-inhibiting effects do not exist. The authors reported on their experience using octreotide in patients with recurrent or unresectable meningiomas of the skull base. Between January 1996 and December 2010, 13 patients harboring a progressive residual meningioma (as indicated by MR imaging criteria) following operative therapy were treated with a monthly injection of the SST analog octreotide (Sandostatin LAR [long-acting repeatable] 30 mg, Novartis). Eight of 13 patients had a meningioma of the skull base and were analyzed in the present study. Post-operative tumor enlargement was documented in all patients on MR images obtained before the initiation of SST therapy. All tumors were benign. No patient received radiation or chemotherapy before treatment with SST. The growth of residual tumor was monitored by MR imaging every 12 months. Three of the 8 patients had undergone surgical treatment once; 3, 2 times; and 2, 3 times. The mean time after the last meningioma operation (before starting SST treatment) and tumor enlargement as indicated by MR imaging criteria was 24 months. A total of 643 monthly cycles of Sandostatin LAR were administered. Five of the 8 patients were on SST continuously and stabilized disease was documented on MR images obtained in these patients during treatment (median 115 months, range of 48 to 180 months). Three of the 8 patients interrupted treatment: after 60 months in 1 case because of tumor progression, after 36 months in 1 case because of side effects, and after 36
months in 1 case because the health insurance company denied cost absorption. The authors concluded that although no case of tumor regression was detected on MR imaging, the study results indicated that SST analogs can arrest the progression of unresectable or recurrent benign meningiomas of the skull base in some patients. It remains to be determined whether a controlled prospective clinical trial would be useful.

In patients with primary cutaneous malignant melanoma, accurate staging of the primary tumor and detection of any occult micro-metastases in the regional lymph node basin is most important in determining survival and successful outcome of treatment. According to accepted guidelines, preoperative cutaneous lymphoscintigraphy can be used to visualize the lymphatic drainage patterns from primary tumors and intraoperative lymphatic mapping can be used to identify the first sentinel lymph node in direct communication with the primary tumor. Only individuals with histologically confirmed sentinel node metastases are selected to undergo radical node dissection and eventually receive adjuvant treatments, sparing those with tumor-free sentinel node the morbidity of these therapies.

In the past, it was routine practice to carry out axillary lymph node dissection at the time of surgical removal of a primary, malignant breast tumor. As breast cancer is being diagnosed at an earlier stage in a growing percentage of cases, this procedure has proven to be unnecessary in a demonstrable proportion of patients. As an alternative management strategy, several authorities have recommended identification of the sentinel node to predict the disease status of the axilla and consequently determine whether axillary lymph node dissection is indicated. This can be accomplished using lymphoscentigraphy or injection of isosulfan blue, or both, followed by biopsy. The sentinel node can be identified in 80% of patients and accurately predicts the status of the remainder of the axillary nodes in 95% to 98% of patients. If the node is negative by frozen section nothing more is done. If it is positive, a standard axillary dissection is done. By limiting the number of lymph nodes removed, the injury to the circulatory system is minimized, and the risk of arm swelling (lymphedema) following treatment for breast cancer may be reduced.

Pheochromocytoma is a rare tumor of catecholamine-secreting chromaffin cells. Several conventional and nuclear imaging modalities are currently available to localize pheochromocytoma. Computed tomography (CT) and magnetic resonance imaging (MRI) have good sensitivity but poor specificity for detecting pheochromocytoma.

I-131 meta-Iodobenzylguanidine (MIBG) is a compound that is actively accumulated in neuroendocrine tumors and thyroid tumors, which express the noradrenaline transporter. While nuclear imaging approaches such as I-131 MIBG imaging have limited sensitivity, the specificity of I-131 MIBG scintigraphy is very good. According to the NCI PDQ Database, CT and MRI scans are about equally sensitive (98 to 100%) for pheochromocytoma, while MIBG scanning has a sensitivity of only 80%. However, MIBG scanning has a specificity of 100%, compared to specificity of 70% for CT and MRI. Thus, I-131 MIBG imaging provides a method for confirming that a tumor is a pheochromocytoma and rules out metastatic disease. Currently, I-131 MIBG is approved as an adjunctive diagnostic agent in the localization of primary or metastatic pheochromocytoma and neuroblastoma. According to the National Cancer Institute’s PDQ Database, for staging of neuroblastoma, bone should be assessed by MIBG scan (applicable to all sites of disease) and by technetium-99 scan if the results of the MIBG imaging are negative or unavailable. MIBG has also been used for detection of other neural crest tumors.
Adrenomedullary imaging can also be performed with I-123 MIBG. Furthermore, I-123 MIBG scintigraphy is also used for characterization of the cardiac nervous system. Cardiac I-123 MIBG imaging, which reflects cardiac adrenergic nerve activity, may provide prognostic information on patients with congestive heart failure. It is also used in the diagnosis of other cardiac diseases such as cardiomyopathy and idiopathic ventricular fibrillation. Prospective randomized controlled studies are needed to ascertain the prognostic value of I-123 MIBG imaging in patients with heart failure and patients at risk for arrhythmia, and how I-123 MIBG imaging may affect management strategy. Furthermore, the FDA has not approved the use of I-123 MIBG for these purposes.

Tamaki et al (2009) compared the predictive value of cardiac I-123 MIBG imaging for sudden cardiac death (SCD) with that of the signal-averaged electrocardiogram (SAECG), heart rate variability (HRV), and QT dispersion in patients with chronic heart failure (CHF). Cardiac MIBG imaging, SAECG, 24-hr Holter monitoring, and standard 12-lead electrocardiography (ECG) were performed in 106 consecutive stable CHF outpatients with a radionuclide left ventricular ejection fraction (LVEF) less than 40 %. The cardiac MIBG washout rate (WR) was obtained from MIBG imaging. Furthermore, the time and frequency domain HRV parameters were calculated from 24-hr Holter recordings, and QT dispersion was measured from the 12-lead ECG. During a follow-up period of 65 ± 31 months, 18 of 106 patients died suddenly. A multi-variate Cox analysis revealed that WR and LVEF were significantly and independently associated with SCD, whereas the SAECG, HRV parameters, or QT dispersion were not. Patients with an abnormal WR (greater than 27 %) had a significantly higher risk of SCD (adjusted hazard ratio: 4.79, 95 % confidence interval: 1.55 to 14.76). Even when confined to the patients with LVEF greater than 35 %, SCD was significantly more frequently observed in the patients with than without an abnormal WR (p = 0.02). The authors concluded that cardiac MIBG WR, but not SAECG, HRV, or QT dispersion, is a powerful predictor of SCD in patients with mild-to-moderate CHF, independently of LVEF. This study has several drawbacks: (i) small and empirically chosen study population sample size and empirically chosen follow-up period length, (ii) single-center study, (iii) patients NYHA functional class IV were not included in the study, and (iv) failure to include data from T-wave alternans testing, which has recently been shown to be useful for the risk stratification of SCD in CHF patients.

On September 19, 2008, the FDA approved iobenguane I-123 injection (AdreView) for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests. Iobenguane accumulates in adrenergically innervated tissues as well as tumors derived from the neural crest. The uptake of iobenguane I-123 by metabolically active neuroblastoma or pheochromocytoma allows scintigraphic visualization of these tumors. The safety and effectiveness of iobenguane I-123 were assessed in a single-arm clinical study of patients with known or suspected neuroblastoma or pheochromocytoma. Diagnostic effectiveness was determined for 211 patients by comparison of focal increased radionuclide uptake on planar scintigraphy at 24 ± 6 hours post-administration of iobenguane I-123 injection against the definitive diagnosis (standard of truth). The standard of truth was a diagnosis of presence or absence of pheochromocytoma in 127 patients and neuroblastoma in 84 patients. The diagnosis was determined by histopathology or, when histopathology was unavailable, a composite of imaging, plasma/urine catecholamine and/or catecholamine metabolite measurements and clinical follow-up. In the detection of either neuroblastoma or pheochromocytoma, the iobenguane I-123's sensitivity and specificity were determined independently based upon results of 3 image-readers who were fully masked to clinical information. The sensitivity
ranged from 77% to 80% and the specificity ranged from 69% to 77%. Performance characteristics were similar between the groups of patients who had either a pheochromocytoma or neuroblastoma truth standard.

The American Academy of Neurology's practice parameter on the diagnosis and prognosis of new onset Parkinson disease (Suchowersky et al, 2006) stated that there is insufficient evidence to determine if I-123 labeled MIBG cardiac imaging is useful in differentiating Parkinson's disease from multiple system atrophy or progressive supranuclear palsy.

According to available guidelines, surgical ablation is the treatment of choice for pheochromocytoma (Sweeney and Blake, 2002). Radiopharmaceutical ablation with MIBG has met with only "limited success" (NCI, 2003). The National Cancer Institute PDQ on pheochromocytoma stated that "treatment with targeted radiation therapy using 1131meta-iodobenzylguanidine (1131 MIBG) has met with limited success. In approximately 35% of patients screened, the tumor has sufficient uptake of the radioisotope to allow for a therapeutic dose. In a group of 28 patients shown to have sufficient uptake of I131 MIBG, objective partial responses were observed in 29% and biochemical improvement was noted in 43%. According to guidelines from the National Comprehensive Cancer Network (2003) on pheochromocytoma, MIBG may be used as an alternative to surgical debulking and medical therapy for persons with distant metastases who are enrolled in a clinical trial (NCCN, 2003).

Quach and colleagues (2011) analyzed the effects of (131) I-MIBG therapy on thyroid and liver function in patients with neuroblastoma. Pre- and post-therapy thyroid and liver functions were reviewed in a total of 194 neuroblastoma patients treated with (131) I-MIBG therapy. The cumulative incidence over time was estimated for both thyroid and liver toxicities. The relationship to cumulative dose/kg of body weight, number of treatments, time from treatment to follow-up, sex, and patient age was examined. In patients who presented with grade 0 or 1 thyroid toxicity at baseline, 12 +/- 4% experienced onset or worsening to grade 2 hypo-thyroidism and 1 patient developed grade 2 hyper-thyroidism by 2 years after (131) I-MIBG therapy. At 2 years post-(131) I-MIBG therapy, 76 +/- 4% patients experienced onset or worsening of hepatic toxicity to any grade, and 23 +/- 5% experienced onset of or worsening to grade 3 or 4 liver toxicity. Liver toxicity was usually transient asymptomatic transaminase elevation, frequently confounded by disease progression and other therapies. The authors concluded that prophylactic regimen of potassium iodide and potassium perchlorate with (131) I-MIBG therapy resulted in a low rate of significant hypo-thyroidism. Liver abnormalities following (131) I-MIBG therapy were primarily reversible and did not result in late toxicity. They stated that (131) I-MIBG therapy is a promising treatment for children with relapsed neuroblastoma with a relatively low rate of symptomatic thyroid or hepatic dysfunction.

Lin et al (1999) discussed the potential diagnostic and therapeutic utility of somatostatin receptor scintigraphy and therapy with somatostatin. In-111 pentetreotide (In-111 octreotide), a somatostatin analog, was used to define the receptor status and the extent of disease in a case of malignant thymoma. Subsequent treatment with non-radioactive somatostatin inhibited tumor growth. The authors concluded that In-111 octreotide may be useful to define tumor receptor status and may provide prognostic information useful in determining subsequent therapy.

In a phase II study, Loehr et al (2004) examined the objective response rate, duration of remission and toxicity of octreotide alone or with the later addition of prednisone in
patients with unresectable, advanced thymic malignancies in whom the pre-treatment octreotide scan was positive. A total of 42 patients with advanced thymoma or thymic carcinoma were entered onto the trial, of whom 38 were fully assessable (1 patient had inconclusive histology; 3 patients had negative octreotide scan). Patients received octreotide 0.5 mg subcutaneously 3 times a day. At 2 months, patients were evaluated. Responding patients continued to receive octreotide alone; patients with progressive disease were removed from the study. All others received prednisone 0.6 mg/kg orally 4 times a day for a maximum of 1 year. Two complete responses ([CR]; 5.3 %) and 10 partial responses ([PR]; 25 %) were observed (4 PR with octreotide alone; the remainder with octreotide plus prednisone). None of the 6 patients without pure thymoma responded. The 1- and 2-year survival rates were 86.6 % and 75.7 %, respectively. Patients with an Eastern Cooperative Oncology Group performance status of 0 lived significantly longer than did those with a performance status of 1 (p = 0.031). The authors concluded that octreotide alone has modest activity in patients with octreotide scan-positive thymoma. Prednisone improves the overall response rate but is associated with increased toxicity. They stated that additional studies with the agent are warranted.

Ozkan et al (2011) evaluated the outcome of high-dose In-111 octreotide treatment and efficacy of long-acting release (LAR) somatostatin in patients with disseminated neuroendocrine tumors. A total of 14 patients (mean age of 51.8 +/- 13.2 years; 4 males and 10 females) receiving high-dose In-111 octreotide for the treatment of neuroendocrine tumors were included in the study. Monthly treatment with long-acting somatostatin analog (somatostatin LAR) was continued in 9 cases. During a 3-year period, a total of 45 courses of high-dose In-111 octreotide treatment were delivered to 14 patients. In 7 patients receiving an average of 4 treatment courses (6 carcinoid tumors, 1 thymoma, patients: 2, 4, 5, 11 to 14) stable disease was achieved (50 %). In 2 patients with carcinoid tumors (patients 1 and 3) who received 4 treatment courses, PR was observed (14 %). Five patients (36 %; 4 NET, 1 gastrinoma; patients 6 to 10) died due to progressive disease following on average 2 treatment courses. On average, deaths occurred 2 months after the last treatment dose. No CR was seen; PR was achieved in 2 of the 9 patients receiving somatostatin LAR, while 4 had stable disease. Both treatments were associated with acceptable tolerability. The authors concluded that high-dose In-111 octreotide can be safely administered in conjunction with somatostatin analog in patients with disseminated NET and this treatment may help to stabilize the disease.

Gubens (2012) noted that thymomas and thymic carcinomas are rare diseases of the anterior mediastinum. Although some thymomas are quite indolent and able to be resected in a curative fashion, the treatment of metastatic disease remains a challenge, especially for the more aggressive thymic carcinoma histology. Based on the results of single-arm trials, combination chemotherapy is the standard of care in the first-line, and anthracycline-based treatments should be used if patients are reasonably fit. Several single-agent cytotoxic chemotherapy agents have some effectiveness in subsequent lines of therapy, especially pemetrexed and, in octreotide scan-positive patients, octreotide. The author stated that prospective trials of new agents are difficult to conduct given the rarity of thymoma, but various targeted therapies do show promise. Greater international research collaboration, as well as modern techniques in molecular and genomic characterization, should help to advance the treatment of thymic malignancies in the near future.

The NCCN clinical practice guideline on “Thymomas and thymic carcinomas” (Version 2.2013) lists etoposide, ifosfamide, pemetrexed, octreotide (LAR; with or without
prednisone), 5-fluorouracil, gemcitabine, and paclitaxel as a second line chemotherapy. It also states that “None of these agents have been assessed in randomized trials. Octreotide may be useful in patients with thymoma who have a positive octreotide scan or symptoms of carcinoid syndrome … Patients with thymoma also have an increased risk for second malignancies, although no particular screening studies are recommended”.

In a prospective study, Berczi and associates (2002) evaluated the effectiveness of technetium-99m-sestamibi and technetium-99m-pertechnetate subtraction scanning and ultrasonography (US) for imaging parathyroid glands in primary hyper-parathyroidism (pHPT). A total of 63 patients were surgically treated for pHPT. Pre-operative scintigraphy and US were performed in all cases. Bilateral neck exploration was carried out on each patient. Results of radionuclide studies and US were compared with surgical and histological findings. In 57 patients with pHPT the radionuclide scanning gave true-positive results. Four false-negative and 2 false-positive scintigrams were obtained. The sensitivity and the positive-predictive value (PPV) of scintigraphy were 93 % and 97 %, respectively. Forty-one cases were correctly localized by the US. A total of 17 US results were false-negative and 5 were false-positive. The sensitivity and the PPV for US were 71 and 89 %, respectively. There was a statistically significant difference between the sensitivity of the scintigraphy compared with the US (p = 0.001). Sensitivities of radionuclide scans and US were higher for adenomas (100 and 83 %) than for hyperplastic glands (75 and 40%). The sensitivity of technetium-99m-sestamibi and technetium-99m-pertechnetate subtraction scintigraphy (SS) was significantly higher compared with US. This sensitive method could help surgeons in performing a rapid and directed parathyroidectomy.

Barczynski and colleagues (2006) determined the sensitivity and PPV of SS versus US of the neck combined with rapid intact parathyroid hormone (iPTH) assay in US-guided fine-needle parathyroid aspirates in pre-operative localization of parathyroid adenomas and in directing surgical approach. The results of SS for localization of parathyroid adenoma were determined in 121 patients with pHPT and compared with findings at surgery and with the results of US alone (in patients without nodular goiter) and US in combination with the iPTH assay in US-guided fine-needle aspirates (FNAs) of suspicious parathyroid lesions (in patients with concomitant nodular goiter). All 121 patients had biochemically documented pHPT; all were referred for first-time surgery. Subtraction scintigraphy was performed with 99mTc-sestamibi and 99mTc-pertechnetate. High-resolution US of the neck was performed by a single endocrine surgeon and combined with US-guided FNAs of suspicious parathyroid lesions in all patients with nodular goiter (n = 43). The sensitivity and PPV of SS were significantly higher in patients without versus with goiter (89.3 % and 95.7 % versus 74.3 % and 76.5 %, respectively; p < 0.001). The sensitivity and PPV of US were significantly higher in patients without versus with goiter (96 % and 97.3 % versus 67.7 % and 71.9 %, respectively; p < 0.001). The iPTH assay of US-guided FNAs of suspicious parathyroid lesions in patients with nodular goiter significantly improved both the sensitivity and PPV of US imaging (90.7 % and 100 %, respectively), allowing for an accurate choice of surgical approach in 118 (97.5 %) of 121 patients. Subtraction scintigraphy was more accurate than US alone in detection of ectopic parathyroid adenomas. However, US alone was characterized by a higher sensitivity in detection of small parathyroid adenomas (less than 500 mg) at typical sites (p < 0.01). The authors concluded that both the sensitivity and PPV of SS and US alone are comparable, with significantly less accurate results obtained in patients with goiter. In cases of equivocal results of US and/or in patients with concomitant goiter, an iPTH assay in US-guided FNAs of suspicious parathyroid lesions may be used to establish the nature of the mass,
distinguish between parathyroid and non-parathyroid tissue (goiter, lymph nodes) and improve the accuracy of US parathyroid imaging, allowing for successful directing of surgical approach in a majority of patients.

Powell et al (2013) evaluated the benefit of adding a pertechnetate parathyroid scan (dual-isotope imaging) in the interpretation of sestamibi dual-phase parathyroid scintigraphy. A total of 116 dual Tc-99m sestamibi (MIBI) and Tc-99m pertechnetate subtraction parathyroid studies, performed between January 2000 and February 2006, were retrospectively reviewed. Dual-phase technetium sestamibi examinations were initially interpreted, with blindling to the technetium pertechnetate findings. Subsequently, pertechnetate scan findings were added, and changes in interpretation were recorded. By adding Tc-99m pertechnetate imaging, the interpretation of 17 scans (17/116 = 14.6 %) was substantially altered. This included 5 scans (4 %) that changed from negative to positive and 9 scans (8 %) that changed from equivocal to positive, excluding ectopic tissue and directing minimally invasive surgery, without the need for further imaging, such as ultrasound, in 12 % of cases. One examination changed from positive to negative. In addition, 2 scans changed from equivocal to negative, necessitating further pre-operative imaging for the evaluation of additional pathology such as thyroid nodules and lymph nodes and the consideration of hyperplasia. Among the remaining 99 patients, Tc-99m pertechnetate scans may also have contributed to the diagnosis in the 66 positive Tc-99m MIBI scans by increasing confidence in the interpretation and obviating additional imaging; 10 cases remained equivocal. The authors concluded that by adding Tc-99m pertechnetate imaging, scan interpretation was changed in 14.6 % of cases, and interpretation confidence was enhanced in all but 10 remaining equivocal cases. The addition of a dual-isotope subtraction also eliminated the need for additional testing, such as ultrasound, in 12 % of our cases. Increased confidence in interpretation that comes with dual-isotope subtraction may come at the cost of slight lengthening of imaging time but likely simplifies pre-operative localization and decreases intraoperative time for many patients with primary hyperparathyroidism.

Also, an UpToDate review on “Preoperative localization for parathyroid surgery in patients with primary hyperparathyroidism” (Yip et al, 2013) states that “Subtraction thyroid scan -- Even with the addition of SPECT, distinguishing abnormal parathyroid glands from thyroid pathology can be difficult. If necessary, a subtraction thyroid scan can be obtained by using two radiotracers (dual isotope scintigraphy). The use of technetium plus a second radiotracer such as 123I or 99mTc pertechnetate (thallium) permits selective imaging of the thyroid gland”.

Moran and Paul (2002) noted that oncogenic hypophosphatemic osteomalacia is a rare condition. The causative tumor is often difficult to locate. Primary tumors have been reported in the head and neck, skeleton, and soft tissue. Octreotide scanning was used in this case and detected a mesenchymal tumor in the pubic symphysis.

Takahashi et al (2008) reported the case of a 31-year old woman with tumor-induced osteomalacia suffering from slowly progressive bilateral muscle weakness predominantly in the proximal muscles and multiple bone pains for the past 2 years. She was unable to walk or raise her arms above the shoulder. These investigators suspected tumor-induced osteomalacia due to decreased serum phosphate and 1alpha, 25 (OH)-vitamin D3 levels, low percentage of tubular reabsorption of phosphate (%TRP), adult onset, and no family history of osteomalacia. Regular imaging examinations could not detect the location of the primary tumor: however, indium-111 octreotide scintigraphy detected the causative
primary mesenchymal tumor in the right sole. Pain and muscle weakness improved promptly after tumor resection, and she was able to walk 6 days post-operatively. This was the first case report in Japan describing the detection of the primary tumor site by indium-111 octreotide scintigraphy.

Seijas et al (2009) noted that oncogenic osteomalacia is a rare paraneoplastic syndrome of acquired hypophosphatemic osteomalacia, resulting from a deficit in renal tubular phosphate reabsorption, in which fibroblast growth factor 23 (FGF23) seems to be implicated. This condition is usually associated with a phosphaturic mesenchymal tumor of mixed connective tissue located in the bone or soft tissue. The clinical and the radiologic findings are the same as those seen in osteomalacia, and the biochemical features include renal phosphate loss, low serum phosphate and 1,25-(OH)(2) vitD(3) levels, increased alkaline phosphatase, and normal calcium, PTH, calcitonin, 25-OH-vitD (3) and 25,25-(OH)(2) vitD(3). These investigators presented 2 cases of oncogenic osteomalacia associated with phosphaturic mesenchymal tumors, which were histologically similar, but presented a completely different evolution. In the first patient, the tumor developed on the sole of the foot. Following removal of the mass, the symptoms resolved and biochemical and radiological parameters returned to normal. However, in the second patient, a liver tumor developed and resection did not resolve the disease. Multiple lesions appeared in several locations during follow-up. This disease usually remits with complete tumor resection. Nevertheless, if this is not possible, oral treatment with phosphate, calcium and calcitriol can improve the symptoms. If scintigraphy of the tumor shows octreotide receptors, patients may respond partially to therapy with somatostatin analogs, with stabilization of the lesion.

Hu et al (2011) stated that tumor-induced osteomalacia (TIO), or oncogenic osteomalacia (OOM), is a rare acquired paraneoplastic disease characterized by renal phosphate wasting and hypophosphatemia. Recent evidence shows that tumor-over-expressed fibroblast growth factor 23 (FGF23) is responsible for the hypophosphatemia and osteomalacia. The tumors associated with TIO are usually phosphaturic mesenchymal tumor mixed connective tissue variants (PMTMCT). Surgical removal of the responsible tumors is clinically essential for the treatment of TIO. However, identifying the responsible tumors is often difficult. These researchers reported a case of a TIO patient with elevated serum FGF23 levels suffering from bone pain and hypophosphatemia for more than 3 years. A tumor was finally located in first metacarpal bone by octreotide scintigraphy and she was cured by surgery. After complete excision of the tumor, serum FGF23 levels rapidly decreased, dropping to 54.7 % of the pre-operative level 1 hour after surgery and eventually to a little below normal. The patient's serum phosphate level rapidly improved and returned to normal level in 4 days. Accordingly, her clinical symptoms were greatly improved within 1 month after surgery. There was no sign of tumor recurrence during an 18-month period of follow-up. According to pathology, the tumor was originally diagnosed as "iomangioma" based upon a biopsy sample, "proliferative giant cell tumor of tendon sheath" based upon sections of tumor, and finally diagnosed as PMTMCT by consultation 1 year after surgery. The authors concluded that although an extremely rare disease, clinicians and pathologists should be aware of the existence of TIO and PMTMCT, respectively.

Jiang et al (2012) noted that TIO is an acquired form of hypophosphatemia. Tumor resection leads to cure. These researchers investigated the clinical characteristics of TIO, diagnostic methods, and course after tumor resection in Beijing, China, and compared them with 269 previous published reports of TIO. A total of 94 patients with adult-onset
hypophosphatemic osteomalacia were seen over a 6-year period (January, 2004 to May, 2010) in Peking Union Medical College Hospital. After physical examination (PE), all patients underwent technetium-99m octreotide scintigraphy ((99) Tc(m)-OCT). Tumors were removed after localization. The results demonstrated that 46 of 94 hypophosphatemic osteomalacia patients had high uptake in (99) Tc(m) -OCT imaging. Forty of them underwent tumor resection with the TIO diagnosis established in 37 patients. In 2 patients, the tumor was discovered on PE but not by (99) Tc(m) -OCT. The gender distribution was equal (M/F = 19/20). Average age was 42 ± 14 years. In 35 patients (90 %), the serum phosphorus concentration returned to normal in 5.5 ± 3.0 days after tumor resection. Most of the tumors (85 %) were classified as phosphaturic mesenchymal tumor (PMT) or mixed connective tissue variant (PMTMCT). Recurrence of disease was suggested in 3 patients (9 %). When combined with the 269 cases reported in the literature, the mean age and sex distribution were similar. The tumors were of bone (40 %) and soft tissue (55 %) origins, with 42 % of the tumors being found in the lower extremities. The authors concluded that TIO is an important cause of adult-onset hypophosphatemia in China; (99) Tc(m)-OCT imaging successfully localized the tumor in the over-whelming majority of patients. Successful removal of tumors leads to cure in most cases, but recurrence should be sought by long-term follow-up.

Sanchez et al (2013) reported the case of an oncogenic osteomalacia in a 50-year-old male. He suffered severe bone pain and marked muscular weakness of 4 years' duration. There were several vertebral deformities in the thoracic spine, bilateral fractures of the ilio-pubic branches, another fracture in the left ischio-pubic branch, and a Looser's zone in the right proximal tibia. An octreotide-Tc scan allowed to identify a small tumor in the posterior aspect of the right knee. It was surgically removed. Microscopically, it was a phosphaturic mesenchymal tumor-mixed connective tissue (PMT-MCT). Expression of FGF-23 was documented by immune-peroxidase staining. There was rapid improvement, with consolidation of the pelvic fractures and the tibial pseudo-fracture. The laboratory values returned to normal.

Jing et al (2013) stated that TIO is an endocrine disorder caused by tumors producing excessive fibroblast growth factor-23 (FGF-23). The causative tumors are generally small, slow-growing benign mesenchymal tumors. The only cure of the disease depends on resection of the tumors, which are extremely difficult to localize due to their small sizes and rare locations. Since these tumors are known to express somatostatin receptors, this research was undertaken to evaluate efficacy of [Tc-99m]-HYNIC-octreotide (99mTc-HYNIC-TOC) whole body imaging in this clinical setting. Images of 99mTc-HYNIC-TOC scans and clinical chart from 183 patients with hypophosphatemia and clinically suspected TIO were retrospectively reviewed. The scan findings were compared to the results of histopathologic examinations and clinical follow-ups. Among 183 patients, 72 were confirmed to have TIO while 103 patients were found to have other causes of hypophosphatemia. The possibility of TIO could not be either diagnosed or excluded in the remaining 8 patients. For analytical purposes, these 8 patients who could neither be diagnosed nor excluded as having TIO were regarded as having the disease, bringing the total of TIO patients to 80. The 99mTc-HYNIC-TOC scan identified 69 tumors in 80 patients with TIO, which rendered a sensitivity of 86.3 % (69/80). 99mTc-HYNIC-TOC scintigraphy excluded 102 patients without TIO with a specificity of 99.1 % (102/103). The overall accuracy of 99mTc-HYNIC-TOC whole body scan in the localization of tumors responsible for osteomalacia is 93.4 % (171/183). The authors concluded that whole body 99mTc-HYNIC-TOC imaging is effective in the localization of occult tumors causing TIO.
Furthermore, an UpToDate review on “Hereditary hypophosphatemic rickets and tumor-induced osteomalacia” (Scheinman and Drezner, 2013) states that “The diagnosis of tumor-induced osteomalacia should be suspected from the clinical constellation of acquired hypophosphatemia and osteomalacia or rickets in association with renal phosphate wasting (but no other proximal tubular defects) and an inappropriately low plasma calcitriol concentration. The phenotype is similar to X-linked and autosomal dominant hypophosphatemic rickets but the family history is negative and the disorder is acquired. Finding the tumors can be a major diagnostic challenge, and may involve total body magnetic resonance imaging (MRI), scintigraphy using octreotide labeled with indium-111 (because the tumors typically express somatostatin receptors), or scintigraphy combined with positron emission tomography/computerized tomography (PET/CT).”

Leong et al (2011) noted that a new low-molecular-weight mannose receptor-based, reticuloendothelial cell-directed, (99m)Tc-labeled lymphatic imaging agent, (99m)Tc-tilmanocept, was used for lymphatic mapping of sentinel lymph nodes (SLNs) from patients with primary breast cancer or melanoma malignancies. This novel molecular species provided the basis for potentially enhanced SLN mapping reliability. In a prospectively planned, open-label phase II clinical trial, (99m)Tc-tilmanocept was injected into breast cancer and cutaneous melanoma patients before intra-operative lymphatic mapping. Injection technique, pre-operative lympho-scintigraphy (LS), and intra-operative lymphatic mapping with a hand-held gamma detection probe were performed by investigators per standard practice. A total of 78 patients underwent (99m)Tc-tilmanocept injection and were evaluated (47 melanoma, 31 breast cancer). For those whom LS was performed (55 patients, 70.5 %), a (99m)Tc-tilmanocept hot spot was identified in 94.5 % of LS patients before surgery. Intra-operatively, (99m)Tc-tilmanocept identified at least 1 regional SLN in 75 (96.2 %) of 78 patients: 46 (97.9 %) of 47 in melanoma and 29 (93.5 %) of 31 in breast cancer cases. Tissue specificity of (99m)Tc-tilmanocept for lymph nodes was 100 %, displaying 95.1 % mapping sensitivity by localizing in 173 of 182 nodes removed during surgery. The overall proportion of (99m)Tc-tilmanocept-identified nodes that contained metastatic disease was 13.7 %. Five procedure-related serious adverse events occurred, none related to (99m)Tc-tilmanocept. The authors concluded that these findings demonstrated the safety and effectiveness of (99m)Tc-tilmanocept for use in intra-operative lymphatic mapping. The high intra-operative localization and lymph node specificity of (99m)Tc-tilmanocept and the identification of metastatic disease within the nodes suggested SLNs are effectively identified by this novel mannose receptor-targeted molecule.

Tokin et al (2012) stated that SLN mapping is common, however question remains as to what the ideal imaging agent is and how such an agent might provide reliable and stable localization of SLNs. (99m)Tc-labeled nanocolloid human serum albumin (Nanocoll) is the most commonly used radio-labeled colloid in Europe and remains the standard of care (SOC). It is used in conjunction with vital blue dyes (VBDs) that relies on simple lymphatic drainage for localization. Although the exact mechanism of Nanocoll SLN localization is unknown, there is general agreement that Nanocoll exhibits the optimal size distribution and radiolabeling properties of the commercially available radiolabel colloids. [(99m)Tc] Tilmanocept is a novel radiopharmaceutical designed to address these deficiencies. These researchers compared [(99m)Tc]Tilmanocept to Nanocoll for SLN mapping in breast cancer. Data from the phase III clinical trials of [(99m)Tc]Tilmanocept's concordance with VBD was compared to a meta-analysis of a review of the literature to identify a (99m)Tc albumin colloid SOC. The primary end-points were SLN localization rate and degree of localization. A total of 6 studies were used for a meta-analysis to identify the colloid-based SOC; 5 studies (6,134 patients) were used to calculate the SOC.
Tumor Scintigraphy

localization rate of 95.91% (Cl: 0.9428 to 0.9754) and 3 studies (1,380 patients) were used for the SOC SLN degree of localization of 1.6683 (Cl: 1.5136 to 1.8230). The lower bound of the confidence interval was used for comparison to Tilmanocept. Tilmanocept data included 148 patients, and pooled analysis revealed a 99.99% (Cl: 0.9977 to 1.0000) localization rate and degree of localization of 2.16 (Cl: 1.964 to 2.3600). The authors concluded that Tilmanocept was superior to the Nanocoll SOC for both end-points (p < 0.0001).

Sondak et al (2013) stated that ([99mTc]Tilmanocept is a CD206 receptor-targeted radiopharmaceutical designed for SLN identification. Two nearly identical non-randomized phase III trials compared ([99mTc]Tilmanocept to VBD. Patients received ([99mTc]Tilmanocept and blue dye. Sentinel lymph nodes identified intra-operatively as radioactive and/or blue were excised and histologically examined. The primary end-point, concordance, was the proportion of blue nodes detected by ([99mTc]Tilmanocept; 90% concordance was the pre-specified minimum concordance level. Reverse concordance, the proportion of radioactive nodes detected by blue dye, was also calculated. The prospective statistical plan combined the data from both trials. A total of 15 centers contributed 154 melanoma patients who were injected with both agents and were intra-operatively evaluated. Intra-operatively, 232 of 235 blue nodes were detected by ([99mTc]Tilmanocept, for 98.7% concordance (p < 0.001). ([99mTc]Tilmanocept detected 364 nodes, for 63.7% reverse concordance (232 of 364 nodes). ([99mTc]Tilmanocept detected at least 1 node in more patients (n = 150) than blue dye (n = 138, p = 0.002). In 135 of 138 patients with at least 1 blue node, all blue nodes were radioactive. Melanoma was identified in the SLNs of 22.1% of patients; all 45 melanoma-positive SLNs were detected by ([99mTc]Tilmanocept, whereas blue dye detected only 36 (80%) of 45 (p = 0.004). No positive SLNs were detected exclusively by blue dye. Four of 34 node-positive patients were identified only by ([99mTc]Tilmanocept, so 4 (2.6%) of 154 patients were correctly staged only by ([99mTc]Tilmanocept. No serious adverse events were attributed to ([99mTc]Tilmanocept. The authors concluded that ([99mTc]Tilmanocept met the pre-specified concordance primary end-point, identifying 98.7% of blue nodes. It identified more SLNs in more patients, and identified more melanoma-containing nodes than blue dye.

Wallace et al (2013) stated that SLN surgery is used world-wide for staging breast cancer patients and helps limit axillary lymph node dissection. In 2 open-label, non-randomized, within-patient, phase III clinical trials, ([99mTc]Tilmanocept was evaluated to assess the lymphatic mapping performance. A total of 13 centers contributed 148 patients with breast cancer. Each patient received ([99mTc]Tilmanocept and VBD. Lymph nodes identified intra-operatively as radioactive and/or blue stained were excised and histologically examined. The primary end-point, concordance (lower boundary set point at 90%), was the proportion of nodes detected by VBD and ([99mTc]Tilmanocept. A total of 13 centers contributed 148 patients who were injected with both agents. Intra-operatively, 207 of 209 nodes detected by VBD were also detected by ([99mTc]Tilmanocept for a concordance rate of 99.04% (p < 0.0001). ([99mTc]Tilmanocept detected a total of 320 nodes, of which 207 (64.7%) were detected by VBD. ([99mTc]Tilmanocept detected at least 1 SLN in more patients (146) than did VBD (131, p < 0.0001). In 129 of 131 patients with greater than or equal to 1 blue node, all blue nodes were radioactive. Of 33 pathology-positive nodes (18.2% patient pathology rate), ([99mTc]Tilmanocept detected 31 of 33, whereas VBD detected only 25 of 33 (p = 0.0312). No pathology-positive SLNs were detected exclusively by VBD. No serious adverse events were attributed to ([99mTc]Tilmanocept. The authors concluded that ([99mTc]Tilmanocept demonstrated success in detecting a SLN while meeting the primary end-point. Interestingly, ([99mTc]Tilmanocept was additionally noted to identify more SLNs in more patients. This localization represented a higher number of metastatic breast cancer lymph nodes than that of VBD.

On March 13, 2013, The FDA approved Lymphoseek (technetium Tc 99m tilmanocept)
Injection for location of lymph nodes in patients with breast cancer or melanoma who are undergoing surgery to remove tumor-draining lymph nodes. The most common side effects identified in clinical trials was pain or irritation at the injection site.

In a prospective, non-randomized, single-arm, part of an ongoing phase III clinical trial, Marcinow et al (2013) evaluated the preliminary utility of technetium Tc 99m (99mTc)-tilmanocept in patients with oral cavity squamous cell carcinoma (OSCC). Patients had previously untreated, clinically and radiographically node-negative OSCC (T1-4aN0M0) at an academic tertiary referral center. Patients received a single dose of 50 µg 99mTc-tilmanocept injected peri-tumorally followed by dynamic planar LS and fused single-photon emission computed tomography/computed tomography (SPECT/CT) prior to surgery. Surgical intervention consisted of excision of the primary tumor and radio-guided SLN dissection followed by planned elective neck dissection (END). The excised lymph nodes (SLNs and non-SLNs) underwent histopathologic evaluation for presence of metastatic disease. Main outcome measures were false-negative rate and negative-predictive value of SLNB using 99mTc-tilmanocept and comparison of planar LS with SPECT/CT in SLN localization. Twelve of 20 patients (60%) had metastatic neck disease on pathologic examination. All 12 had at least 1 SLN positive for metastases. No patients had a positive END node who did not have at least 1 positive SLN. These data yielded a false-negative rate of 0% and negative-predictive value of 100% using 99mTc-tilmanocept in this setting. Dynamic planar LS and SPECT/CT revealed a mean (range) number of hot spots per patient of 2.9 (1-7) and 3.7 (1-12), respectively. Compared with planar LS, SPECT/CT identified additional putative SLNs in 11 of 20 cases (55%). The authors concluded that the high negative-predictive value and low false-negative rate in identification of occult metastases shows 99mTc-tilmanocept to be a promising agent in SLN identification in patients with OSCC. Use of SPECT/CT improved pre-operative SLN localization including delineation of SLN locations near the primary tumor when compared with planar LS imaging.

Ma and colleagues (2014) compared the potential application of (99m)Tc-3P-Arg-Gly-Asp ((99m)Tc-3P4-RGD2) scintimammography (SMM) and (99m)Tc-methoxyisobutylisonitrile ((99m)Tc-MIBI) SMM for the differentiation of malignant from benign breast lesions. A total of 36 patients with breast masses on physical examination and/or suspicious mammography results that required fine needle aspiration cytology biopsy (FNAB) were included in the study. (99m)Tc-3P4-RGD2 and (99m)Tc-MIBI SMM were performed with SPECT at 60 mins and 20 mins, respectively, after intravenous injection of 738 ± 86 MBq radiotracers on a separate day. Images were evaluated by the tumor to non-tumor localization ratios (T/NT). Receiver operating characteristic (ROC) curve analysis was performed on each radiotracer to calculate the cut-off values of quantitative indices and to compare the diagnostic performance for the ability to differentiate malignant from benign diseases. The mean T/NT ratio of (99m)Tc-3P4-RGD2 in malignant lesions was significantly higher than that in benign lesions (3.54 ± 1.51 versus 1.83 ± 0.98, p < 0.001). The sensitivity, specificity, and accuracy of (99m)Tc-3P4-RGD2 SMM were 89.3%, 90.9% and 89.7%, respectively, with a T/NT cut-off value of 2.40. The mean T/NT ratio of (99m)Tc-MIBI in malignant lesions was also significantly higher than that in benign lesions (2.86 ± 0.99 versus 1.51 ± 0.61, p < 0.001). The sensitivity, specificity and accuracy of (99m)Tc-MIBI SMM were 87.5%, 72.7% and 82.1%, respectively, with a T/NT cut-off value of 1.45. According to the ROC analysis, the area under the curve for (99m)Tc-3P4-RGD2 SMM (area = 0.851) was higher than that for (99m)Tc-MIBI SMM (area = 0.781), but the statistical difference was not significant. The authors concluded that (99m)Tc-3P4-RGD2 SMM does not provide any significant advantage over the established (99m)Tc-MIBI SMM for the detection of primary breast cancer. The T/NT ratio of (99m)Tc-3P4-RGD2 SMM was significantly higher than that of (99m)Tc-MIBI SMM. Both tracers could offer an alternative method for elucidating non-diagnostic mammograms.
Sharma et al (2014) evaluated the diagnostic utility of a single vial ready to label with [99mTc] kit preparation of DTPA-bis-methionine (DTPA-bis-MET) for the detection of primary breast cancer. The conjugate (DTPA-bis-MET) was synthesized by covalently conjugating 2 molecules of methionine to DTPA and formulated as a single vial ready to label with [99mTc] lyophilized kit preparations. A total of 30 female patients (mean age of 47.5 ± 11.8 years; range of 21 to 69 years) with radiological/clinical evidence of having primary breast carcinoma were subjected to [99mTc]-methionine scintigraphy. The whole body (anterior and posterior) imaging was performed on all the patients at 5 mins, 10 mins, 1 hr, 2 hrs, and 4 hrs following an intravenous administration of 555 to 740 MBq radioactivity of [99mTc]-methionine. In addition, scintimammography (static images; 256 × 256 matrix) at 1, 2, and 4 hrs was also performed on all the patients. The resultant radiolabel, that is, [99mTc]-DTPA-bis-MET, yielded high radiolabeling efficiency (greater than 97.0%), radiochemical purity (166 to 296 MBq/µmol), and shelf-life (greater than 3 months). The radiotracer primarily was excreted through the kidneys and localized in the breast cancer lesions with high target-to-nontarget ratios. The mean ± SD ratios on the scan-positive lesions acquired at 1, 2, and 4 hrs post-injection were 3.6 ± 0.48, 3.10 ± 0.24, and 2.5 ± 0.4, respectively. [99mTc]-methionine scintimammography demonstrated an excellent sensitivity and positive predictive value of 96.0 % each for the detection of primary breast cancer. The authors concluded that ready to label single vial kit formulations of DTPA-bis-MET can be easily synthesized in house production and conveniently used for the scintigraphic detection of breast cancer and other methionine-dependent tumors expressing the L-type amino acid transporter-1 receptor. The imaging technique thus could be a potential substitute for the conventional SPECT-based tumor imaging agents, especially for tracers with non-specific mitochondrial uptake. However, they stated that the diagnostic efficacy of [99mTc]-methionine needs to be evaluated in a large cohort of patients through further multi-centric trials.

Liu et al (2014) explored the diagnostic performance of 99mTc-3(poly-(ethylene glycol),PEG)-4-RGD2 (99mTc-3PRGD2) SMM in patients with either palpable or non-palpable breast lesions and compared SMM to mammography to assess the possible incremental value of SMM in breast cancer detection. These researchers also investigated the αvβ3 expression in malignant and benign breast lesions. A total of 94 patients with 110 lesions were included in this study. Mammograms were evaluated according to the Breast Imaging Reporting and Data System (BI-RADS) by a specialized imaging radiologist. Prone SMM was performed 1 hour after injection of 99mTc-3PRGD2. Scintigraphic images were interpreted independently by 2 experienced nuclear medicine physicians using a 3-point system, and the kappa value was calculated to determine the inter-reader agreement. The McNemar test was used to compare SMM and mammography with respect to sensitivity, specificity, and accuracy. Diagnostic values for breast cancer detection were evaluated for each lesion. Immunohistochemistry was performed to evaluate integrin αvβ3 expression. Histopathology revealed 46 malignant lesions and 64 benign lesions. The overall sensitivity, specificity, accuracy, PPV, and negative-predictive value (NPV) of SMM were 83 %, 73 %, 77 %, 69 %, and 85 %, respectively. The kappa value between the 2 reviewers was 0.63. The diagnostic values of SMM were higher than those of mammography in evaluating overall breast lesions. A sensitivity of 91 % was achieved when SMM and mammography results were combined with 60 % of all false-negative mammography findings classified as true-positive results by SMM. Integrin αvβ3 expression was positively identified using SMM imaging. The authors concluded that SMM is a promising tool to avoid unnecessary biopsies when used in addition to mammography and can be used to image αvβ3 expression in breast cancer with good image quality.
**Tumor Scintigraphy:**

CPT codes covered if selection criteria are met for ProstaScint, Oncoscint, CEA-Scan, Technetium-99m-Sestamibi Scintigraphy, OctreoScan, Radiolabeled Octreotide, Meta-Iodobenzylguanidine (MIBG), and Breast Specific Gamma imaging:

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**ProstaScint:**

**HCPCS codes covered if selection criteria are met:**

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**ICD-9 codes covered if selection criteria are met:**

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<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>V10.46</td>
<td>Personal history of malignant neoplasm of prostate</td>
</tr>
</tbody>
</table>

**Oncoscint:**

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4642</td>
<td>Indium In-111 satumomab pendetide, diagnostic, per study dose, up to 6 millicuries</td>
</tr>
</tbody>
</table>

**ICD-9 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>153.0 - 153.9</td>
<td>Malignant neoplasm of colon</td>
</tr>
<tr>
<td>154.0 - 154.8</td>
<td>Malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
</tr>
<tr>
<td>183.0</td>
<td>Malignant neoplasm of ovary</td>
</tr>
<tr>
<td>V10.05</td>
<td>Personal history of malignant neoplasm of large intestine</td>
</tr>
<tr>
<td>V10.06</td>
<td>Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
</tr>
<tr>
<td>V10.43</td>
<td>Personal history of malignant neoplasm of ovary</td>
</tr>
</tbody>
</table>

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>172.0 - 172.9</td>
<td>Malignant melanoma of skin</td>
</tr>
<tr>
<td>174.0 - 175.9</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>185</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>200.00 - 202.88</td>
<td>Lymphosarcoma and reticulosarcoma</td>
</tr>
</tbody>
</table>
Tumor Scintigraphy

340 Multiple sclerosis
429.2 Cardiovascular disease, unspecified
453.0 - 453.9 Other venous embolism and thrombosis
490 - 496 Chronic obstructive pulmonary disease and allied conditions
555.0 - 556.9 Regional enteritis and ulcerative colitis
714.0 - 714.9 Rheumatoid arthritis and other inflammatory polyarthropathies
V76.0 - V76.9 Special screening for malignant neoplasms

Other ICD-9 codes related to the CPB:

795.79 Other and unspecified nonspecific immunological findings

CEA-Scan:

HCPCS codes covered if selection criteria are met:

A9568 Technetium Tc-99m ariculumab, diagnostic, per study dose, up to 45 millicuries

ICD-9 codes covered if selection criteria are met:

153.0 - 153.9 Malignant neoplasm of colon
154.0 - 154.8 Malignant neoplasm of rectum, rectosigmoid junction, and anus
V10.05 Personal history of malignant neoplasm of large intestine
V10.06 Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus

Technetium-99m-Sestamibi Scintigraphy:

HCPCS codes covered if selection criteria are met:

A9500 Technetium Tc-99m sestamibi, diagnostic, per study dose, up to 40 millicuries
A9512 Technetum tc-99m pertechnetate (thallium) subtraction scan

HCPCS codes not covered for indications listed in the CPB:

S8080 Scintimammography (radioimmunoscintigraphy of the breast), unilateral, including supply of radiopharmaceutical

ICD-9 codes covered if selection criteria are met:

170.0 - 170.9 Malignant neoplasm of bone and articular cartilage
171.0 - 171.9 Malignant neoplasm of connective and other soft tissue
193 Malignant neoplasm of thyroid gland
226 Benign neoplasm of thyroid glands
227.1 Benign neoplasm of other endocrine glands and related structures, parathyroid gland

V10.87 Personal history of malignant neoplasm of thyroid

ICD-9 codes not covered for indications listed in the CPB:

174.0 - 175.9 Malignant neoplasm of breast
191.0 - 192.9 Malignant neoplasm of brain and other and unspecified parts of nervous system
196.3 Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb
198.3 Secondary malignant neoplasm of brain and spinal cord
198.4 Secondary malignant neoplasm of other parts of nervous system
198.81 Secondary malignant neoplasm of breast
225.0 - 225.9 Benign neoplasm of brain and other parts of nervous system
233.0 Carcinoma in-situ of breast
237.0 - 237.6 Neoplasm of uncertain behavior of endocrine glands and nervous system

OctreoScan:

HCPCS codes covered if selection criteria are met:

A9572 Indium In-111 pentetrotide, diagnostic, per study dose, up to 6 millicuries

ICD-9 codes covered if selection criteria are met:

157.0 - 157.9 Malignant neoplasm of pancreas [VIPoma, Islet cell tumors]
192.1 Malignant neoplasm of cerebral meninges [meningioma]
193 Malignant neoplasm of thyroid gland
194.0 Malignant neoplasm of adrenal gland [paragangliomas, pheochromocytomas]
194.3 Malignant neoplasm of pituitary gland and craniopharyngeal duct
194.6 Malignant neoplasm of aortic body and other paraganglia
201.00 - 201.98 Hodgkin's disease
209.00 - 209.16 Malignant carcinoid tumor of small intestine
209.20 - 209.29 Malignant carcinoid tumor of other and unspecified sites
Tumor Scintigraphy

209.30 Malignant poorly differentiated neuroendocrine tumors
209.40 - 209.69 Benign carcinoid tumor
211.1 Benign neoplasm of stomach
211.6 Benign neoplasm of pancreas, except islets of Langerhans
211.7 Benign neoplasm of Islets of Langerhans [gastrinomas, glucagonomas, Islet cell tumors]
225.2 Benign neoplasm of cerebral meninges [menigioma]
225.4 Benign neoplasm of spinal meninges
227.0 Benign neoplasm of adrenal gland [paragangliomas, pheochromocytomas]
227.3 Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)
227.6 Benign neoplasm of aortic body and other paraganglia
235.2 Neoplasm of uncertain behavior of stomach, intestines, and rectum
235.5 Neoplasm of uncertain behavior of other and unspecified digestive organs
235.7 Neoplasm of uncertain behavior of trachea, bronchus, and lung
237.0 Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
237.2 Neoplasm of uncertain behavior of adrenal gland
237.3 Neoplasm of uncertain behavior of paraganglia
237.4 Neoplasm of uncertain behavior of other and unspecified endocrine glands
237.6 Neoplasm of uncertain behavior of meninges
259.2 Carcinoid syndrome
275.8 Disorders of calcium metabolism, other specified disorders of mineral metabolism [tumor-induced osteomalacia TIO [oncogenic osteomalacia]]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

135 Sarcoidosis
160.0 Malignant neoplasm of nasal cavities [neuroblastoma]
162.2 - 162.9 Malignant neoplasm of bronchus and lung [small-cell lung cancer]
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>164.0</td>
<td>Malignant neoplasm of thymus [thymoma]</td>
</tr>
<tr>
<td>164.2 - 164.9</td>
<td>Malignant neoplasm of mediastinum [neuroblastoma]</td>
</tr>
<tr>
<td>173.0 - 173.9</td>
<td>Malignant neoplasm of skin [Merkel cell tumors]</td>
</tr>
<tr>
<td>190.0 - 190.9</td>
<td>Malignant neoplasm of eye [ocular melanoma]</td>
</tr>
<tr>
<td>191.0 - 191.9</td>
<td>Malignant neoplasm of brain [astrocytoma]</td>
</tr>
<tr>
<td>192.0</td>
<td>Malignant neoplasm of cranial nerves [neuroblastoma, olfactory]</td>
</tr>
<tr>
<td>194.0</td>
<td>Malignant neoplasm of adrenal gland [neuroblastoma]</td>
</tr>
<tr>
<td>194.6</td>
<td>Malignant neoplasm of aortic body and other paraganglia [chemodectomas]</td>
</tr>
<tr>
<td>197.0</td>
<td>Secondary malignant neoplasm of lung</td>
</tr>
<tr>
<td>197.1</td>
<td>Secondary malignant neoplasm of mediastinum</td>
</tr>
<tr>
<td>197.3</td>
<td>Secondary malignant neoplasm of other respiratory organs</td>
</tr>
<tr>
<td>197.8</td>
<td>Secondary malignant neoplasm of other digestive organs and spleen</td>
</tr>
<tr>
<td>198.2</td>
<td>Secondary malignant neoplasm of skin</td>
</tr>
<tr>
<td>198.3</td>
<td>Secondary malignant neoplasm of brain and spinal cord</td>
</tr>
<tr>
<td>198.4</td>
<td>Secondary malignant neoplasm of other parts of nervous system</td>
</tr>
<tr>
<td>198.7</td>
<td>Secondary malignant neoplasm of adrenal gland</td>
</tr>
<tr>
<td>200.00 - 200.88, 202.00 - 208.92</td>
<td>Malignant neoplasm of lymphatic and hematopoietic tissue [except Hodgkin's]</td>
</tr>
<tr>
<td>209.17</td>
<td>Malignant carcinoid tumor of the rectum [neuroendocrine carcinoma of the rectum]</td>
</tr>
<tr>
<td>211.7</td>
<td>Benign neoplasm of Islets of Langerhans [insulinomas]</td>
</tr>
<tr>
<td>212.6</td>
<td>Benign neoplasm of thymus [thymoma]</td>
</tr>
<tr>
<td>227.6</td>
<td>Benign neoplasm of aortic body and other paraganglia [chemodectomas]</td>
</tr>
</tbody>
</table>

**Radiolabeled Ocreotide:**

**There is no specific code for radiolabeled octreotide:**

**ICD-9 codes covered if selection criteria are met :**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>209.00 - 209.30</td>
<td>Malignant carcinoid tumor</td>
</tr>
<tr>
<td>209.40 - 209.69</td>
<td>Benign carcinoid tumor</td>
</tr>
</tbody>
</table>

http://qawww.aetna.com/cpb/medical/data/100_199/0168_draft.html 03/25/2015
ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

192.1  Malignant neoplasm of cerebral meninges [meningioma]
225.2  Benign neoplasm of cerebral meninges [meningioma]

**Lymphoscintigraphy and Sentinel Lymph Node Biopsy:**

CPT codes covered if selection criteria are met:

38500 - 38530  Biopsy or excision of lymph node(s)
38792  Injection procedure; radioactive tracer for identification of sentinel node
+38900  Intraoperative identification (eg, mapping) of sentinel lymph node(s), includes injection of non-radioactive dye, when performed
78195  Lymphatics and lymph nodes imaging

ICD-9 codes covered if selection criteria are met:

172.0 - 172.9  Malignant melanoma of skin
174.0 - 175.9  Malignant neoplasm of breast
198.81  Secondary malignant neoplasm of breast
233.0  Carcinoma in-situ of breast

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

V84.01  Genetic susceptibility to malignant neoplasm of breast [BRCA1 or BRCA2 mutations confirmed by molecular susceptibility testing for breast cancer]

**I-131 labeled Meta-Iodobenzylguanidine (MIBG) Imaging:**

HCPCS codes covered if selection criteria are met:

A9508  Iodine I-131 iobenguane sulfate, diagnostic, per 0.5 millicurie

ICD-9 codes covered if selection criteria are met:

192.0  Malignant neoplasm of cranial nerves [neuroblastoma]
193  Malignant neoplasm of thyroid gland
194.0  Malignant neoplasm of adrenal gland [localizing or confirming neuroblastoma or pheochromocytoma] [paraganglioma]
194.5  Malignant neoplasm of carotid body [paragangliomas]
194.6  Malignant neoplasm of aortic body and other paraganglia [paragangliomas]
209.00 - 209.30 Malignant carcinoid tumor
209.40 - 209.69 Benign carcinoid tumor

227.0 Benign neoplasm of adrenal gland [pheochromocytomas] [paraganglioma]
227.5 Benign neoplasm of carotid body [paragangliomas]
227.6 Benign neoplasm of aortic body and other paraganglia [paragangliomas]

235.2 Neoplasm of uncertain behavior of stomach, intestines, and rectum
235.5 Neoplasm of uncertain behavior of other and unspecified digestive organs

237.2 Neoplasm of uncertain behavior of adrenal gland
237.3 Neoplasm of uncertain behavior of paraganglia
237.4 Neoplasm of uncertain behavior of other and unspecified endocrine glands

255.8 Other specified disorders of adrenal glands [adrenal medulla hyperplasia]
259.2 Carcinoid syndrome

**I-131 labeled Meta-Iodobenzylguanidine (MIBG) Radiotherapy:**

**CPT codes not covered for indications listed in the CPB:**

79005 Radiopharmaceutical therapy, by oral administration
79101 Radiopharmaceutical therapy, by intravenous administration
79300 Radiopharmaceutical therapy, by interstitial radioactive colloid administration
79403 Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion
79445 Radiopharmaceutical therapy, by intra-arterial particulate administration

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

194.0 Malignant neoplasm of adrenal gland [neuroblastoma, pheochromocytoma]
227.0 Benign neoplasm of adrenal gland [pheochromocytoma]

**I-123 Injection for Imaging:**

**HCPCS codes covered if selection criteria are met:**
A9582  Iodine I-123 iobenguane, diagnostic, per study dose, up to 15 millicuries

**ICD-9 codes covered if selection criteria are met (not all-inclusive):**

194.0  Malignant neoplasm of adrenal gland [for the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests]

**ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):**

249.00 - 249.91  Secondary diabetes mellitus
250.00 - 250.93  Diabetes mellitus
332.0 - 332.1  Parkinson's disease
333.0  Other degenerative diseases of the basal ganglia [progressive supranuclear palsy]
357.2  Polyneuropathy in diabetes
362.01 - 362.07  Anterior and posterior subcapsular polar cataract
366.41  Diabetic cataract
401.0 - 405.99  Hypertensive disease
410.00 - 414.9  Ischemic heart disease
425.4  Other primary cardiomyopathies
427.0 - 427.9  Cardiac dysrhythmias
428.0  Congestive heart failure
V42.1  Heart replaced by transplant
V58.69  Long-term (current) use of other medications

**Scintimammography and Breast Specific Gamma Imaging (BSGI):**

**CPT codes not covered for indications listed in the CPB:**

78195  Lymphatics and lymph nodes imaging
78800  Radiopharmaceutical localization of tumor or distribution of radiopharmaceutical agent(s); limited area
78801  multiple areas
78803  tomographic (SPECT)

**HCPCS codes not covered for indications listed in the CPB:**
A9500  Technetium Tc-99m sestamibi, diagnostic, per study dose, up to 40 millicuries

S8080  Scintimammography (radioimmunosintigraphy of the breast), unilateral, including supply of radiopharmaceutical

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

174.0 - 175.9  Malignant neoplasm of the breast

195.1  Malignant neoplasm of thorax [axilla]

198.81  Secondary malignant neoplasm of the breast

198.89  Secondary malignant neoplasm of other specific sites [axillary metastases]

233.0  Carcinoma in situ of breast

234.8  Carcinoma in situ of other specified sites [axilla]

V76.10 - V76.19  Special screening examination for malignant neoplasms of breast

**Technetium-Tc 99m Tilmanocept (Lymphoseek):**

HCPCS codes covered if selection criteria are met:

A9520  Technetium Tc-99m tilmanocept, diagnostic, up to 0.5 millicuries

ICD-9 codes covered if selection criteria are met:

172.0 - 172.9  Malignant melanoma of skin

174.0 - 174.9  Malignant neoplasm of female breast

175.0 - 175.9  Malignant neoplasm of male breast

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

141.0 - 145.9  Malignant neoplasm of oral cavity

The above policy is based on the following references:

ProstaScint


OncoScint


CEA Scan


10. Medical Services Advisory Committee (MSAC). CEA-Scan for imaging recurrence and/or metastases in patients with histologically demonstrated carcinoma of the colon or rectum. MSAC application 1062. Canberra, ACT: Medical Services Advisory Committee (MSAC); 2004:1-98.

Scintimammography and Breast Specific Gamma Imaging (BSGI)


OctreoScan and OctreoTher


47. Scheinman SJ, Drezner MK. Hereditary hypophosphatemic rickets and tumor-induced osteomalacia. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed November 2013.


Lymphoscintigraphy


Meta-Iodobenzylguanidine (MIBG) Imaging


AndreView


Technetium-Tc 99m Tilmanocept:


